THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JANUARY, 1945

ORIGINAL ARTICLES

DIABETES MELLITUS AS OBSERVED IN 100 CASES FOR 10 OR MORE YEARS

I. General Observations

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This paper, and those immediately following, present a study in this clinic of 100 patients, with diabetes for 10 years or more. This investigation was undertaken because these patients have been under close supervision in the clinic for many years and because, during these years, they have been maintained on a diet in which the carbohydrate has been increased and the fat decreased, compared with diets previously in general use. We do not know of other investigations based on material of this nature, all studied for more than 10 years.

It seemed also that examinations of the heart, eyes and peripheral circulation in these patients, over a period of years, might add to our knowledge of the influence of long-standing diabetes on these organs.

Certain observations are given regarding the diet and insulin prescribed and the complications encountered in these patients.

Methods. The patients in this series comprise the first 100 persons, with diabetes of more than 10 years duration, who made clinic visits after the investigation was started. Some of them had attended the clinic for many years, while others had only recently completed 10 years of treatment when reviewed by us.

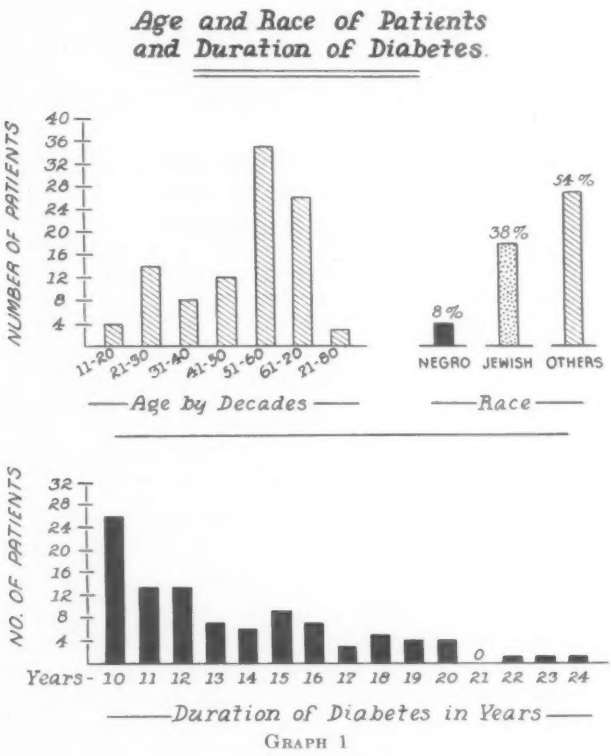
They were first examined in the Metabolic Clinic and were then referred to the Cardiac, the Peripheral Vascular and the Ophthalmologic Clinics. Examinations in these clinics were made with especial reference to the diabetes.

During the past 15 years or more these patients had been taking a diet in which the fat varied between 70 and 110 gm., with an average of about 90 gm., and the carbohydrate had been between 125 and

XUM

200 gm. The protein formerly had been given as 1 gm. per kilo of body weight. This has been gradually increased during recent years to an average of a little over 70 gm. daily.

The blood sugar determinations were done by the method of Folin and Malmros[1] adapted to the Evelyn photoelectric colorimeter, and the cholesterol determinations by a modification of Bloor's method.[2]



GRAPH 1

Age Distribution by Decades and Duration of Diabetes. In Graph 1 is shown the age distribution of these patients at the time of study according to decades. As is usually the case in diabetes, the greater number is found in the later decades of life. Men comprised 25% and women 75% of the group. The distribution of these patients according to race and the duration of diabetes is also shown in Graph 1. Although the 26 patients with diabetes for exactly 10 years make up the largest single group, 74% of the total number had diabetes for a still longer time.

TABLE 1.—BODY WEIGHT OF PATIENTS IN THIS SERIES

Weight	No. patients
More than 10% below normal	15
10% below to 10% above normal	67
11% above to 20% above normal	9
More than 20% above normal	9

Body Weight of Patients. In this clinic every attempt has been made to keep the patients' weight a few pounds below the normal for height, sex and age. In Table 1 is shown the weight of the patients in this series at the end of the 10 year period.

Of these patients, 82 maintained a satisfactory weight for diabetic patients, and 18 were above normal. This far from ideal figure is in part explained by the ignorance of the markedly overweight patients, though it still remains a blot on the educational record.

Heredity. On careful questioning, it appears that only 49% of this group knew of any relatives with diabetes. The familial incidence is probably too low, as relatives of many of the patients were still in Europe and accurate information was not obtainable, and because the history of familial diabetes is less adequate in adults than in children, who were few in this series.

Hospitalization. It has been the rule of this clinic to hospitalize all patients having severe complications or other acute conditions. Other patients were taken into the wards for adjustment of the diet and insulin and for instruction, as accommodations allowed. Of the group, 61% have at some time been taken into the wards, while 39% have been controlled by visits to the clinic without any stay in the hospital.

Acidosis. Acidosis with coma has been present in the histories of 26 of the patients. Most of these occurred before the patient came under the care of the clinic. Of the 26 patients, 17 had acidosis more than 10 years ago, 6 had acidosis at the time when diabetes was diagnosed, and 3 during the past 10 years. All of these recovered. The patients are taught that acidosis is probably the most dangerous of the complications of diabetes.

In addition to the 3 patients who had acidosis and coma during the past 10 years, 3 others had this condition while attending the clinic before that period. All but one of these occurred before the patients were 20 years old. Three of them had acidosis before their 10th year of age, 1 at 18 and 1 at 19 years of age. One woman developed acidosis at 55 with a carbuncle on her neck. All of these patients are now living and doing well.

Severity and Control of Diabetes. In order to investigate any possible influence exerted by the severity of the diabetes or by the effectiveness of its control, these patients have been arranged under both categories. As there is no satisfactory criterion of the severity of the diabetes, we have used the daily insulin requirement for this purpose. By this means we have divided the patients into 4 groups. In the 1st group are included those who took no insulin; in the 2nd group those using up to 25 units daily; in the 3rd group are those taking from 25 to 50 units; while the 4th group consists of those patients who required 50 or more units daily.

In a similar manner, they have also been divided into 4 groups on the basis of the control of diabetes. This has been determined by the averages of all blood sugar determinations made during the years 1934 and 1939, these 2 years being arbitrarily selected. In each patient,

XUM

16 or more blood sugar determinations were used to obtain each of these averages.

The 1st group includes those patients whose average blood sugar for the years stated was below 140 mg. per 100 cc.; in the 2nd those with average blood sugars between 140 and 180; the 3rd group, those from 180 to 250; and the 4th group those with average blood sugar determinations of 250 mg. per 100 cc. or more. In Table 2 are shown the number of patients in each of these groups.

TABLE 2.—CORRELATION BETWEEN THE DEGREE OF DIABETES AND ITS CONTROL

Degree of diabetes in terms of insulin requirement (units per day)	% of cases	% of cases	State of control of diabetes in terms of range of blood sugar (mg. per 100 cc. blood)
None	19	20	<140
5–24	31	40	140–180
25–49	22	32	181–250
50 or more	28	8	>250

It will be noted that all degrees of diabetes are well represented. As regards the diabetic control, it will be seen that 60% of the patients have maintained averages of blood sugar under 180 mg., which is generally considered to represent a fairly satisfactory state of adjustment. Only 8% of them are in what might be considered a poor state of adjustment. It appears from the figures in this table that the most severe diabetics have developed greater skill and care in their control.

Review of the records of these 8 patients fails to show any higher incidence of complications than has been present in patients who maintained a satisfactory diabetic adjustment. The group, however, is too small to allow any definite conclusions to be drawn.

Using the above classifications, the severity of the diabetes and the state of adjustment have been related to the duration of the diabetes. The factor of duration of diabetes apparently has no relation to its severity or to the success with which the patient maintains control.

Change in Patients After 5 Year Period. In order to determine what changes might have occurred in the patients and in our treatment of them over a period of years, certain data were collected. The data shown in Table 3 were taken from the records of 2 separate years, which were 5 years apart. The years selected were 1934 and 1939. The figures given are averages of all observations made during these 2 years. All patients had had diabetes for at least 5 years before the first observations shown in the table.

TABLE 3.—CHANGE IN 100 PATIENTS AFTER A SELECTED 5 YEAR PERIOD

	Year	
	1934	1939
Average diet:		
Protein	68	73
Fat	81	82
Carbohydrate	142	162
Number taking insulin	55	79
Average insulin dose per patient (units)	51	55
Average blood sugar (mg. per 100 cc.)	192	157
Average serum cholesterol (mg. per 100 cc.)	286	237

The average blood sugar and serum cholesterol figures show that there was a slight but definite improvement in the control of all patients in the group. These averages appeared to result from the improvement of the diabetes in some of the patients, and from the better adjustment with increased use of insulin in others. Although both of these factors were evident, it was not possible to separate them for statistical study.

Of the 55 patients taking insulin at the beginning of the 5 year period, 10 took less insulin, 24 took the same amount, and 21 required more insulin at the end than at the beginning of the 5 years. Of the 45 patients who took no insulin at the beginning, 21 still did not require it at the end of the period, while 24 began the use of insulin during the 5 year period.

On studying the data in these histories, it is evident that some of the insulin which was added was for the purpose of maintaining a lower average blood sugar, and others for supporting a larger average diet, especially in carbohydrate, in order to promote the patient's well being. The 24 patients who began taking insulin during the 5 year period were taking an average of 30 units daily at the end of the period.

It is evident that, although the diabetes was progressive in some of the group, it was not by any means always so. In those requiring no increase in the amount of insulin and in those taking no insulin at the end of the period (45 in number), the diabetes certainly had not progressed noticeably. Of the patients whose insulin dosage was increased, a considerable number also had increases in diet.

Infection. In this investigation "infection" has been interpreted either as long-continued, chronic infection, or as repeated acute infections. These diagnoses were made in the wards or by other clinics to which the patients had been referred for examination and treatment (Table 4). According to this classification, 61% of these patients were found to have been free from infection, while 39% had infections during the 10 year period.

In Table 4 are shown the figures for the chronic infections found in these patients.

TABLE 4

Infections	Incidence
Chronic pyelonepritis	9
Chronic cholecystitis	16
Tuberculosis	9
Syphilis	5

The acute infections were not common, and those usually found were pneumonia or abscesses. Acute sinus infections and acute appendicitis occurred occasionally. In a survey of the group, it was evident that some patients remained entirely free of infection, while others were subject to repeated infections of one kind or another. The acute infections often occurred in those patients who had also a chronic infection.

A comparison was made between the presence of infection and the age of the patient, the duration and the severity of the diabetes and

XUM

the state of adjustment of the diabetic condition of the patients. None of these appeared to show any correlation with the incidence of either acute or chronic infection. This result might perhaps be expected in such a group. Although there is considerable variation in the state of adjustment between the different patients, none of them were in such poor diabetic condition as would be commonly found in uncontrolled diabetes in which infection is more frequently present.

It is not known whether the duration of the diabetes influences the susceptibility of the body to infection. It appears, however, from these patients, that any such influence does not increase beyond the 10th year after the onset of diabetes. These patients with diabetes of 10 or more years duration show no increased incidence of infection with increased duration of diabetes.

Syphilis. Syphilis has been diagnosed and treated in 5 of these patients—4 by the Department of Dermatology and Syphilology of this hospital. Four of them at present show no clinical evidence of syphilis. One is now being studied with the possibility that syphilitic aortitis may be present. Three of the 5 patients still show a positive Wassermann reaction, although they have no clinical symptoms and have had extensive treatment.

Tuberculosis. In 9 patients, tuberculosis of the lungs has been confirmed by roentgenograms of the chest. The age of the patients varied between 28 and 62 years. Healed tuberculosis was diagnosed in 2 of the older patients. All except 1 of the others, after having been followed for a number of years, now show a quiescent condition. One man, 35 years old, developed tuberculosis 7 years ago, 5 years after the onset of diabetes. After a long-continued therapeutic pneumothorax treatment, his tuberculosis now seems to be arrested. At the present time he is working and doing well. No other tuberculosis was found in any of these patients.

Arteriosclerosis. Arteriosclerosis of heart and extremities in this group is discussed in the following papers. A search was made in the physical examination for any evidence of a generalized arteriosclerosis. Some evidence was found in 66 of the group. However, in only 9 was this evidence sufficient to indicate a definite clinical entity. Of these 3 were men and 6 were women. Two of these patients were between 50 and 60, and 7 were over 60 years of age. In only 2 patients under the age of 40 was there any evidence of a generalized arteriosclerosis, and in neither of these was it of marked degree. No amputations were done on any of the patients included in this study.

Thyroid. The accelerating action of hyperthyroidism on the metabolism of the diabetic makes the coincident occurrence of these 2 conditions difficult to control. Among this group of patients, 7 women have developed hyperthyroidism, all having been operated on successfully. All of these patients showed some improvement of the diabetes after operation. One non-toxic enlargement also occurred. Including these patients, 42% of the whole group were found, on physical examination, to have at least a slight enlargement of the thyroid, even though, in most of them, no physical signs accompanied it. In this

XUM

group there are 10 men, though in none of them was the enlargement more than minimal and no signs of hyperthyroidism were present in any of them.

Liver. The liver was palpable in 31% of this group, though in only 4 could it be considered a definite enlargement. No clinical symptoms of disease of the liver were found in any of these patients and no extensive studies of liver function were made.

Gall Bladder. The condition of the gall bladder is of interest in diabetes on account of its proximity to the pancreas and on account of the various attempts in the past to connect it with the etiology of diabetes. Of the 16 patients with gall bladder disease, there were 7 with gall stones, on 4 of whom successful cholecystectomies were done. The 3 remaining patients with a diagnosis of gall stones refused operation. However, they improved for a long time on low fat diets. The remaining 84 patients showed no evidence of gall bladder disease. The diagnoses of chronic cholecystitis and cholelithiasis were confirmed by cholecystogram.

Anemia. Examination for anemia was made by erythrocyte counts, and determinations of hemoglobin. These examinations showed that 74% of the group had more than 4,500,000 R.B.C. per cmm. and 14.5 gm. of hemoglobin per 100 gm. of blood. Of the 26 below these figures, only 3 had less than 4 million cells and 13.7 gm. of hemoglobin. It would seem that, on the whole, these patients maintained their blood in almost as satisfactory a condition as non-diabetics. Two patients with primary pernicious anemia are doing well under the combined treatment of both diseases. No significant differences were found in these patients compared with non-diabetics.

Kidney Disease. The incidence of kidney disease other than pyelonephritis has been variously reported from different clinics.[3] We have not made a complete study of the kidneys in this group of patients. However, 29 of them have shown albumin with casts in the urine on several examinations. These are present most frequently in the older patients in whom this finding might be expected. Of 25 patients below 41 years of age, only 2 have albumin in the urine. These are both men, 24 and 31 years old. One man and one woman in the 5th decade (both 48 years old) also have these findings. It would seem that nephritis is little, if any more, frequent in these diabetic patients than in non-diabetics within the same age limits.

Patellar and Babinski reflexes were found, during recent physical examinations, to be normal in 63% and absent in 15%. In the other 22% they were present, though diminished.

Summary. 1. A study is presented of 100 patients with diabetes of 10 or more years duration. The age and race distribution of these patients is that usually found in diabetes.

2. Observations on these patients show that diabetes does not always progress to greater severity. After comparing the diet and insulin at the beginning and at the end of a 5 year period, it is evident that the diabetes of 45% of the patients had not advanced. Ten of these patients required less insulin at the end than at the beginning

XUM

of the period. Of the 55 who required more insulin, a number had also received increases in diet.

3. Acidosis occurred in 3 of the group during the past 10 years.

4. While arteriosclerosis was present in a number of the patients, no amputations were done on any of them.

5. Anemia of a mild degree was present in 26 patients. However, only 3 had less than 4 million R.B.C. and less than 13.5 gm. of hemoglobin per 100 mg. of blood.

6. Chronic or repeated acute infections have been present in 39 patients. Of the former, cholecystitis (16 cases), pyelonephritis (9 cases), and tuberculosis (9 cases) were most frequently encountered.

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DIABETES MELLITUS AS OBSERVED IN 100 CASES FOR 10 OR MORE YEARS

II. Cardiac Studies

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The unusually high incidence of coronary sclerosis and its complications in diabetics, treated with high fat, low carbohydrate diet, as compared to non-diabetics is a well known clinical fact and has been attested by numerous pathologic studies.

This is not the place to enter into detailed discussion of the cause of arteriosclerosis in diabetes. Leary[10] states that excess cholesterol is the cause of the arteriosclerosis which is clinically significant, *i. e.*, sclerosis of the coronary, peripheral and cerebral vessels. Clinical study suggests that the degree of arteriosclerosis is in some way associated with the degree of hypercholesterolemia.[2]

The finding of a direct relationship between hypercholesterolemia and arteriosclerosis in diabetics suggested that the high incidence of the latter may have been due, to some extent at least, to the high fat content of the older diets. Nearly all available statistics are those obtained during the period preceding the high carbohydrate, low fat era. Joslin *et al.*[9] state that since the newer diets "the postponement of premature arteriosclerosis has already begun. No longer does the statement hold that premature arteriosclerosis can be found postmortem in all cases of diabetes of 5 years duration." The purpose of this study is the determination of the status of the heart and aorta of patients who have been on the high carbohydrate low fat diet for at least 10 years.

Material. This study includes 100 patients, all of whom have been known to have diabetes for at least 10 years; the longest 27 years, the average duration was 13.7 years.

Age: The youngest patient was 14 years, the oldest 75 years. The majority, however, were between 50 and 70 years of age. Thirty-one were under 50 years of age and 69 were 50 years or older (Fig. 2).

Sex: Seventy-six were females and 24 were males. However, sex was more evenly divided in the group younger than 50, there being 13 males and 18 females. In the older group females predominated—58 to 11.

Color: There were 7 Negroes in the entire group and of these 6 were females. The remainder were white.

Symptomatology. Forty-five persons presented no cardiac complaints; 26 (57.8%) of the 45 were under 50 years of age and, of these, examination was entirely negative in 19. Only 19 (27.5%) of the older age group were free of symptoms, but only 4 of this group were negative on examination; 13 of the remaining 15 had slight or moderate hypertension.

The most common complaints were weakness and fatigue, which were present in 27 cases; palpitation was the main complaint in 13 instances. Seventeen patients had dyspnea, especially on exertion, and 4 of these complained of nocturnal dyspnea. In 3 of the latter patients, hypertension was marked, and in the 4th there was evidence of severe myocardial damage and marked enlargement of the heart. Edema of the ankles was present in 8 cases but in 4 there were marked varicosities which could account, in part at least, for the edema.

Eight had angina pectoris and 5 other patients had indefinite chest pain. All belonged to the older age group and of the 8 with angina pectoris there were 4 men and 4 women. The 5 cases with indefinite chest pain were women.

The history or ECG suggested that coronary occlusion had occurred in 4 instances, but definite electrocardiographic evidence was obtained in only 1. Two of the 4 cases had angina pectoris and are included in the group above.

Hypertension. Thirty-eight of the entire group had a systolic blood pressure of 160 or more.* Examination of Figure 1 shows that all patients with hypertension were over 50 years of age, representing 55.1% of this group; there was not a single case under 50, and only 1 of the latter had a blood pressure over 150. The greatest incidence was found in the patients between 60 and 70 years, but the percentage increased with each decade (Fig. 2). Nineteen had a systolic blood pressure between 160 and 180, and 19 over 180; the highest recorded systolic pressure being 260. Only 3 (9.1%) of the 38 patients with hypertension were males, although men composed 18.6% of the group past 50; therefore, in this group hypertension was twice as common in females as in males.

* Inasmuch as no case of a high diastolic pressure (100 mg. Hg or higher) was noted without an associated high systolic pressure, for purposes of simplicity and comparison with other similar studies, only systolic pressure will be discussed.

XUM

The orthodiagram disclosed cardiac enlargement in 10 of the 38 cases with hypertension; questionable enlargement in 4 and normal size in 24. In the 19 cases with systolic blood pressure over 180, 6 showed enlargement of cardiac area varying from 11 to 33%; 1 with questionable enlargement and in 12 cardiac area was within normal limits. The aorta was considered abnormal (dilated, elongated or calcified) in 16 patients. In the group with a systolic pressure of at least 180, the aorta in 9 was considered abnormal and in 10 normal. Seven of the 16 with abnormal aortas also showed cardiac enlargement, 7 normal sized hearts and 2 were questionable.

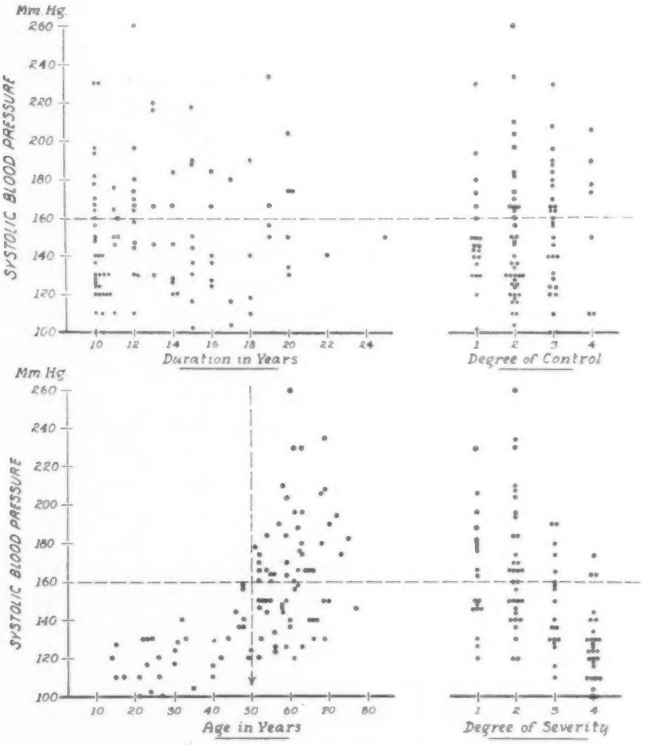

FIG. 1.—The influence of age, duration, severity and ability to control diabetes, upon the systolic blood pressure. The criteria for determining severity and ability to control the diabetic state are explained in Table 2 (page 4) in the first article of this series.

Examinations of the ECGs of the 38 cases failed to disclose a tracing of the type frequently associated with long standing hypertension. Inverted or diphasic T waves in Lead 1 were observed in only 2 cases, and in these the systolic blood pressure was 166 and 170. T waves less than 2 mm. in amplitude were observed in 7 cases; in 2 instances the systolic pressure ranged between 160 and 170, in 3 between 180 and 190, and in 2 over 190. Inversion of the T waves in one or more chest leads was present in 4 instances, the systolic pressures being 166, 170, 178 and 234.

Electrocardiographic Changes. Fifty-nine of the ECGs were normal except for left axis deviation or extrasystoles; normal ECGs were observed in 25 (80.6%) of the group below 50 years and 34 (49.3%) of those above 50 years.

Arrhythmias: Auricular fibrillation was observed in only 2 cases, 1 of these had exophthalmic goiter, the other rheumatic heart disease with mitral stenosis; both were in the older age group. The only other arrhythmia noted was ventricular extrasystoles, which was noted in 7 cases, but in only 2 were they numerous.

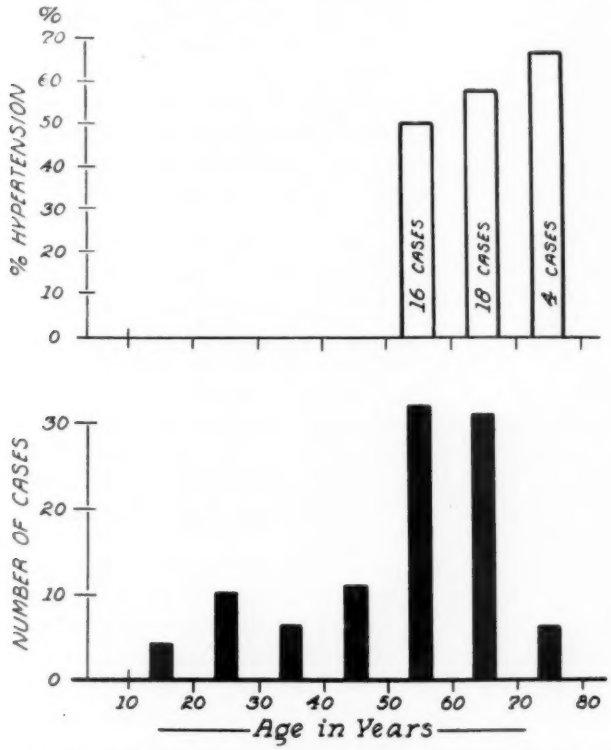

FIG. 2.—The age distribution of 100 cases of diabetes mellitus of at least 10 years' duration and the incidence of hypertension according to decades.

QRS Complex Changes: Two cases showed left bundle branch block and 4 marked intraventricular conduction defects. All were older than 50 years and 5 of the 6 patients had hypertension.

In 23 cases the QRS complexes were slurred in 2 or more leads; in 16 the slurring was slight, in 4 moderate and in 3 slurring was marked. One additional case showed splintering of the QRS complexes in Lead 1 and another in Lead 2.

T Wave Changes: Four cases showed T wave inversion in Lead 1 and in another the T wave was diphasic. In these 5 cases the T wave in CR-5 was also inverted. Six other patients showed inverted or

diphasic T waves in 1 or more chest leads. Two of the 6 were 23 and 15 years of age, the remainder were more than 50 years of age.

Cardiac Size. In determining cardiac enlargement, the tables of Hodges and Eyster[7] were used; cardiac area was considered normal if the computed area was plus or minus 10% of the predicted normal for height and weight. Cardiac area was within normal limits in 66 of the 100 cases; 9 were considered doubtful because the area was in the uppermost limit of normality. In 9 cases the area was smaller than average, the smallest being 28% below the predicted normal. In only 16 cases was cardiac area definitely above normal; the largest cardiac area was 54% above the predicted value. Only 3 of the 25 cases with enlarged or top normal hearts were under 50 years of age; 14 (56%) of this group of 25 had hypertension, although it is interesting that only 26.3% of the hypertensive group showed cardiac enlargement and 10.5% were doubtful. Five of the 6 cases with bundle branch block or severe intraventricular conduction defects showed cardiac enlargement of 16, 17, 20, 30 and 54%; in the other case cardiac area was normal.

Aorta. The ascending aorta was measured in one of the oblique views and the descending portion of the arch was measured by the Kreuzfuchs method. The limitations of both methods are appreciated, and the accuracy of the results obtained are therefore open to question. However, study of our material showed that in 24 the aorta was abnormal in that it was dilated and/or markedly elongated, or showed areas of calcification; in 76 the aorta could not be considered abnormal; although changes were observed in some they were commensurate with the age of the patient. All patients with abnormal aortas were older than 50 years of age, the percentage increasing with each decade and most (66.6%) had hypertension.

Discussion. Although the number of cases in this study is not large, and, as a result, deductions cannot be regarded as conclusive, nevertheless, certain observations merit discussion, namely:

(*a*) The infrequency of hypertension in the group under 50 years of age.

(*b*) In the group of 38 hypertensives, the comparatively low incidence of cardiac enlargement and the absence of ECG changes often observed in hypertension.

(*c*) The frequency of cardiac enlargement in patients (with or without hypertension) with definite ECG evidence of myocardial abnormality.

(*d*) The comparatively small number of patients in the younger aged group with evidence of cardiovascular abnormalities which could be attributed to diabetes. In most cases, with the possible exception of those in the younger age group, the available data does not permit a comparison of the cardiovascular status during the period the patients were on the two types of diet, consequently the influence, if any, of each upon the cardiovascular system cannot be differentiated.

(*a*) Bell and Clawson[2] considered that hypertension was about 2.7 times as common in diabetics as in non-diabetics and, among 175

patients examined postmortem at the Deaconess Hospital, Root and Sharkey[13] found 54% had had a blood pressure between 150 and 230. In our group of 100 cases, 38 had a blood pressure 160 or more; the highest being 260, and 10 others had a blood pressure between 150 and 160; therefore, 48% had a blood pressure over 150.

However, an examination of these cases disclosed certain interesting and pertinent facts. All cases of hypertension (160 mg. Hg) occurred in individuals past 50 years of age (Fig. 1), after which age the incidence increased with each decade and was twice as common in women than men. Figure 1 also suggests that the incidence of hypertension does not appear to be dependent upon the severity, control or duration of diabetes. The high incidence of hypertension in elderly diabetic females is striking, but the interesting observations of Arnett[1] show that hypertension is very common in elderly females; in an old ladies home 56 or 74.8% inmates between the ages of 62 and 95 had a blood pressure over 160 and, of these, 32 or 42.7% had a systolic blood pressure over 180. However, most observers state that hypertension is more common in diabetics than in non-diabetics, although Wilder[16] and also Donhoffer and Szabo[4] believe there is no difference in incidence. In 1929, Major[11] concluded that the blood pressure in diabetics was higher than in normal people of comparable ages, but the incidence of hypertension (150 mg. Hg) increased with age from 5.5% in the group between 35 and 40 to 77% in the group between 70 and 75. In the group between 40 and 45, 25.8% had a blood pressure over 150, and 29.9% in the group between 45 and 50. In our group the incidence increased with each decade (Fig. 2), but only 1 case under 50 years had a systolic blood pressure over 150. In Friedman's[6] series of 120 cases, permanent hypertension (over 150) was found in 30% of the group between 40 and 50 years. Although our group below 50 years comprised but 31 cases, the absence of systolic blood pressure readings over 160 and but a single case over 150, is significant, especially when compared with other series of diabetics who were treated with the older high fat, low carbohydrate diets. What rôle, if any, the high carbohydrate-low fat diet played in reducing the incidence of hypertension in the younger age group, however, is open to speculation.

(*b*) A comparison of ECG and fluoroscopic abnormalities in our group of hypertensives disclosed significant differences when compared to non-diabetic hypertensives. Various clinical studies upon the heart size in hypertension show that cardiac enlargement is present in at least two-thirds of all cases,[15] although methods of determining cardiac enlargement varies. In an unpublished study of 123 hypertensives (systolic blood pressure of 160 or over), including 10 with diabetes, 77 or 62.6% showed definite enlargement of cardiac area. In our group of 38 diabetics with a systolic blood pressure of 160 or over, only 10 (26.3%) showed enlargement of the cardiac area, 4 (10.5%) were doubtful, and 24 (63.2%) showed hearts of normal size. These figures suggest that cardiac enlargement in hypertension is twice as common in non-diabetics as in diabetics. The findings are apparently consistent with

those of Root and Sharkey,[13] who examined the postmortem records of 175 diabetic patients (treated by the older methods) at the New England Deaconess Hospital and found advanced coronary sclerosis in 60 of 93 cases with hypertension, but the striking feature was the lack of hypertrophy except in those cases with preëxisting hypertension.

Although significant changes are found in some of the ECGs of hypertensive diabetics, in none of the 38 cases was the ECG of the type frequently seen in long-standing hypertension and ascribed to left ventricular hypertrophy and by some to left ventricular strain. The 19 patients with a systolic blood pressure of 180 or more failed to show T-1 inversion, and some of these patients were known to have hypertension for a period of at least 10 years. The absence of the typical pattern of the so-called hypertensive ECG is consistent with the comparatively small number of hypertensives with cardiac enlargement compared to non-diabetics, although we are cognizant of the fact that hypertrophy may occur without enlargement of the cardiac silhouette. Although we have observed the hypertensive pattern in cases of hypertension in diabetics not included in this study, nevertheless it must be admitted that our group of 38 is too small to be conclusive and further study will be necessary before any definite conclusion can be drawn.

(*c*) All of the hypertensives were in the older age group, and in the majority the onset of diabetes was before the age of 50 and occurred in the high fat-low carbohydrate era—a period during which all clinical and pathologic studies attested to the frequency of arteriosclerosis in diabetes of 5 years duration, regardless of age. In the majority of cases there are no records of blood pressure readings during this period, but the available data indicates that in some, at least, blood pressure readings have shown a gradual elevation. It is highly probable, therefore, that in many cases arteriosclerosis preceded the hypertension, a sequence of events which Root and Sharkey believe may explain the absence of constant or marked hypertrophy in diabetic hypertensives. However, our data show a low incidence of ECG changes, indicative of myocardial abnormality in hypertensives without cardiac enlargement, and conversely a high incidence of cardiac enlargement in patients whose ECGs show definite evidence of myocardial abnormality with or without hypertension. In the majority of cases (64.7%) with definite electrocardiographic evidence of myocardial abnormality, with or without hypertension, the heart was enlarged or showed questionable enlargement, compared to 36.8% of the group of hypertensives. In only one of the latter was there evidence of severe myocardial abnormality in the ECG associated with a normal sized heart. Cabot[3] found 39% of 631 patients with uncomplicated arteriosclerosis to have cardiac enlargement, and although statistics obtained clinically cannot be compared accurately with those obtained from autopsy material, our data suggests the possibility that in diabetics, cardiac enlargement is frequently associated with arteriosclerosis. The low incidence of cardiac enlargement and

apparent arteriosclerosis in the younger group (under 50) with long-standing diabetes is strong suggestive evidence that present forms of treatment may be responsible for the reduction of premature arteriosclerosis, coronary disease and cardiac enlargement. The importance of adequate glycogen supply to the heart is well known, as is the fact the glycogen synthesis in the heart depends upon blood sugar concentration and insulin in the presence of sufficient oxygen. G. T. Evans[5] has demonstrated in the rat's heart that, by increased insulin and glucose, the normal values of glycogen may be increased so that the heart becomes its own storehouse. One may, therefore, speculate as to whether in the human the high carbohydrate diet with insulin may not also augment the glycogen content and, if given before the advent of advanced sclerosis, increase cardiac efficiency so as to prevent undue left ventricular strain in the presence of hypertension.

(*d*) The comparatively small number of patients under 50 (average age 31.7 years) with cardiac abnormalities which could be attributed to their diabetic state appears significant. Although the duration of diabetes in this group was 10 to 22 years (average 12.9 years), 24 (77.4%) of the 31 cases showed no definite evidence of disease of the heart or aorta clinically, orthodiagraphically or electrocardiographically. Included in the group of abnormal cases are 3 with rheumatic heart disease and 1 case of doubtful etiology. The 3 patients (9.7%) with cardiac abnormalities which could be attributed to their diabetic state, were aged 24, 30 and 47 years with diabetes of 15, 16 and 15 years duration, respectively. Another patient, a woman of 43 years with diabetes of 22 years duration, is known to have peripheral vascular disease; therefore 4 (13%) of the 31 cases under 50 years have cardiovascular abnormalities which could be attributed to their diabetic state. On the older diets, Shepardson[14] found 36% of 50 cases with an average age of 23.4 years with diabetes of at least 5 years duration to have cardiovascular disease, and Rabinowitch[12] stated 80% of patients with diabetes of 5 years or more, regardless of age, had cardiovascular disease.

All studies indicate the high incidence of angina pectoris and/or coronary occlusion in diabetes. Our study also shows a high incidence —11.6% of the group over 50 and 8% of the entire group—but it is worthy of note that the age and the ratio of men to women (5 to 1) in the older age group is comparable to that of the non-diabetics with angina pectoris. However, the number of cases of angina pectoris and/or coronary occlusion is not sufficiently large to be conclusive.

Summary and Conclusions. 1. The cardiovascular status of 100 diabetics who have been on a high carbohydrate-low fat diet for at least 10 years was studied. Sixty-nine of this group were over 50 years of age, and 31 under 50.

2. Hypertension (systolic blood pressure 160 mm. Hg) was present in 38% of the cases. All cases with hypertension were past 50 years of age; the incidence increased with each decade and was twice as common in women as men. The incidence of hypertension apparently was not dependent upon duration, control or severity of the diabetes.

3. Cardiac enlargement was present in 10 of the 38 cases with hypertension, 4 were doubtful and 24 showed hearts of normal size. This incidence of cardiac enlargement is about one-half that observed in non-diabetic hypertensives.

4. The greatest degree of cardiac enlargement was observed in cases with ECG evidence of myocardial abnormality (with or without hypertension), and conversely there was a low incidence of ECG changes indicative of myocardial abnormality in the hypertensives without cardiac enlargement.

5. An ECG of the type frequently seen in hypertension and ascribed to left ventricular hypertrophy or to left ventricular strain was not observed in any of the 38 cases with hypertension.

6. Only 3 (9.7%) patients under 50 had abnormalities of the heart which could be attributed to their diabetic state. The 3 patients were aged 24, 30 and 47 years with diabetes of 15, 16 and 15 years, respectively.

7. The low incidence of cardiovascular abnormalities in the younger group compared to similar studies in the literature on a high fat-low carbohydrate diet is suggestive evidence of the value of the high carbohydrate-low fat diet in reducing the incidence of premature cardiovascular abnormalities.

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DIABETES MELLITUS AS OBSERVED IN 100 CASES FOR 10 OR MORE YEARS

III. Ocular Findings

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This report concerns examination of 100 diabetic patients who have been carefully observed for a period of 10 or more years. These patients were under the care of Dr. Russell Richardson, Chief of the Metabolic

Division of the University Hospital and his staff. They were chosen by the Diabetic Staff for their ability to coöperate in their treatment.

The care and therapy of these patients has been described in the paper of Drs. Richardson and Bowie[1] and will not be repeated.

Method. At the end of 10 years of adequate Out-Patient Department treatment, the eyes of these patients were carefully examined and the following examinations were made:

1. *Visual Acuity* with best possible correction; patients under 45 years received a cycloplegic refraction; those above 45 years a manifest refraction.
2. *Extra-ocular Movements*—for paralysis of individual muscles and conjugate movements.
3. *Pupils*—for reaction to light and accommodation.
4. *Cornea*—(*a*) For wrinkling of Descement's membrane.
   (*b*) Pigment deposition on posterior surface.
5. *Iris*—for depigmentation and signs of old iritis.
6. *Lens*—for opacities, employing a slit-lamp, all pupils were fully dilated and examined for:
   (*a*) Anterior cortical spicules or spokes.
   (*b*) Posterior cortical spicules or spokes.
   (*c*) Subcapsular flaking, anterior or posterior.
   (*d*) Nuclear sclerosis.
   (*e*) Fissures of anterior or posterior cortex.
7. *Intra-ocular Tension*—wherever questionable a tonometer was used.
8. *Retina*—was scrutinized for:
   (*a*) Punctate and superficial hemorrhage.
   (*b*) Exudates of waxy or cotton wool type.
   (*c*) Vessels were examined for any sign of sclerosis or hypertension.
9. *The Optic Nerve*—was viewed with atrophy and neuritis in mind. Any questionable case had a peripheral and central field with white and colored test objects.

These structures were examined because they have been shown by Waite and Beetham[6] to reveal the most frequent abnormalities in diabetic eyes.

TABLE 1.—COMPARISON OF INCIDENCE OF OCULAR FINDINGS IN DIABETICS AND NON-DIABETICS

	This series (%)	Waite and Beetham's diabetic patients (%)	Waite and Beetham's non-diabetic patients (%)
Wrinkles in posterior layer of cornea	8	26.0	10.5
Corneal pigmentation of posterior surface	16	11.8	5.7
Depigmentation of iris epithelium	7	6.0	2.0
Iritis	1	1.3	1.3
Tension	1	0.5	
Pupil reactions sluggish to light	4	2.8	3.5
Extra-ocular muscle palsies	5	4.0	0.1
Optic atrophy	1	0.6	0.4

Waite and Beetham[6] reported a comparative study of 2002 diabetics and 457 non-diabetics. Their diabetic patients varied widely in age and in the duration of the disease. Although therapy was administered to all of their patients, many patients were examined either shortly before or shortly after treatment had been started. The findings they presented may therefore be used to express the incidence of ocular findings in diabetics who have not necessarily been controlled for any

definite period. Thus, their data can be compared to the results of this series of diabetics that has been closely observed and treated for 10 years, and will be a relative means of evaluating the effect of this form of therapy. (See Table 1.)

In reviewing Table 1 it is evident that there is little variation between these 10-year treated diabetics and the cases reported by Waite and Beetham. The one major exception is the wrinkling in the posterior layer of the cornea, the incidence in the 10-year treated cases being much less than in Waite and Beetham's cases. Corneal pigmentation still remains greater, in spite of 10 years of therapy, than in the non-diabetic. This is the same for depigmentation of iris epithelium. There was no greater incidence of iritis, of increased intra-ocular tension, sluggish pupils, nor optic atrophy. It is worthy of mention that in the 24 cases with clinical evidence of pains in the extremities, not one showed evidence of either optic or retrobulbar neuritis. The incidence of extra-ocular muscle palsies was greater in this 10-year treated group, but every one of those cases had a history of onset of palsy prior to the starting of 10-year therapy.

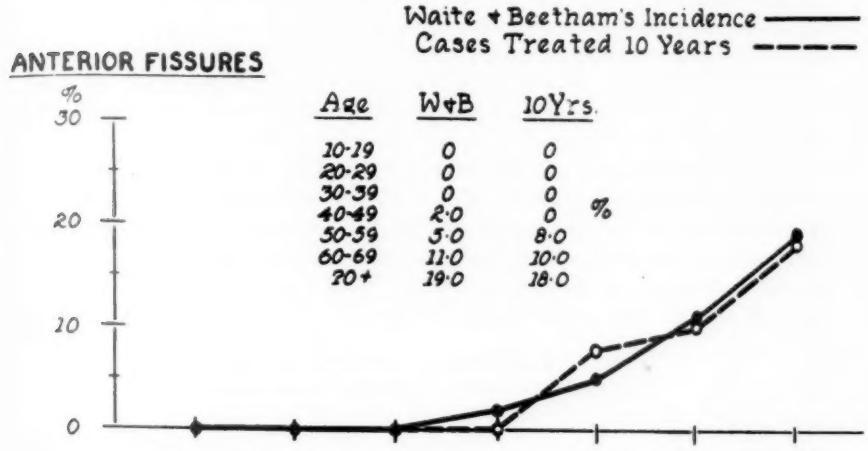
Andersen,[1] in 1925, and Gradle,[2] in 1926, published statistics as to the incidence of lens changes in the population at large after 40 years of age. (See Table 2.) The incidence of spicules, punctate spots, fissures, nuclear sclerosis, and all opacification of lens except subcapsular flocculi in the 10-year group showed a striking similarity to Gradle and Andersen's figures.

TABLE 2.—INCIDENCE OF LENS AND RETINAL CHANGES

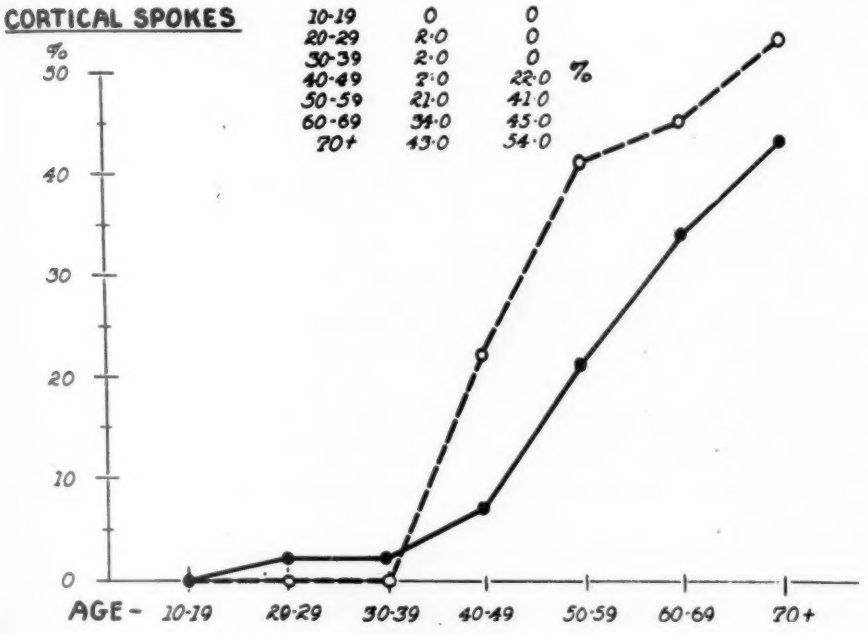
Incidence of lens changes				Incidence of retinal changes in relation to grade of sclerosis		
					Retinal changes	
Decade	Andersen (%)	Gradle (%)	This series (%)	Grade	Punctate retinal hemorrhages (%)	Exudates (%)
41–50	38.2	34.1	33	0	4.5	9
51–60	65.0	66.2	70	1	36.0	26
61–70	85.0	68.4	79	2	41.0	36
70 up	92.0	90.0	90	3	50.0	40
				4	100.0	100

Anterior cortical spokes and spicules of the 10-year treated series can be compared with the diabetics of Waite and Beetham. The same thing can be done with fissures. A glance at these 2 graphs (1 and 2) shows that the fissures in all instances are strikingly parallel, whereas anterior cortical spokes are slightly greater in the 10-year cases. In analyzing this fact, it is wise to remember that Waite and Beetham's figures are based on 4001 diabetic eyes, more than 50% of which were of less than 5 years duration, while in this series all cases have gone over 10 years. The graph, therefore, indicates a greater incidence of anterior cortical spokes in 10-year cases than in those of shorter duration. Waite and Beetham have already shown this fact that spokes in diabetics increase with duration of diabetes and that, in their cases of 10 to 15 years duration, 27% showed anterior cortical spokes. In

these cases, all over 10 years, 32% showed anterior cortical spokes. It can, therefore, be stated that the treatment this group has received has not significantly altered the incidence of anterior cortical spokes.



GRAPH 1.—Incidence of anterior fissures. The data in Graphs 1 to 6 are compared to those of Waite and Beetham.[2]

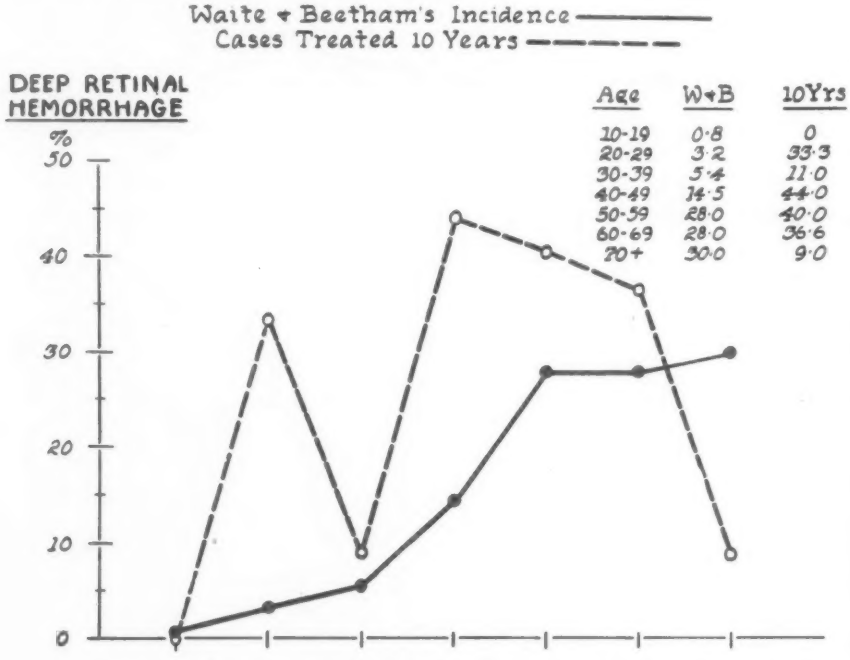


GRAPH 2.—Incidence of cortical spokes.

A similar approach for posterior cortical spokes led to the same conclusion.

The incidence of subcapsular flocculi was 5% in this series. O'Brien,

Molsberry and Allen[3] found 12 snow-flaked cataracts in 126 patients, approximate incidence 10%. They concluded that poorly controlled diabetes, especially if severe and prolonged, was the rule in these cases. This would seem to indicate that therapy has helped to reduce the incidence of the so-called typical diabetic cataract. Likewise, in Waite and Beetham's cases, many of which were of shorter duration than 10 years, and most of which had some form of therapy for varying lengths of time, the incidence of flocculi cataracts was 4%. It would, therefore, seem that therapy tends to reduce the incidence of subcapsular flocculi, not to eliminate it entirely. It may also be that therapy prevents progression of flocculi in some cases. In this series, the incidence of nuclear sclerosis showed no striking variation from incidence of sclerosis in the non-diabetic. There was 1 case of complicated cataract in this series, while Waite and Beetham had 6%; therapy might have reduced the incidence.

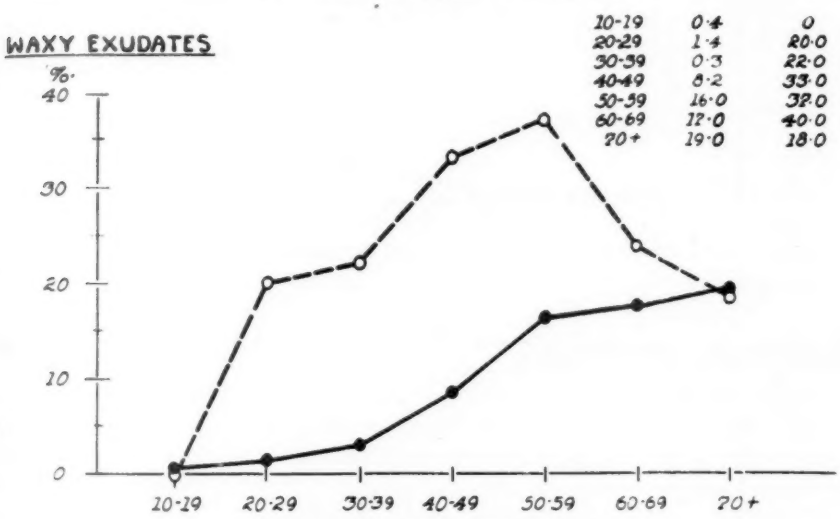


GRAPH 3.—Incidence of deep retinal hemorrhage.

Sclerosis of retinal vessels showed a striking similarity in incidence in the 10-year cases to Waite and Beetham's reported diabetics. It is well to remember that Waite and Beetham's diabetics had sclerosis practically identical in grade and kind to a control series of non-diabetics. It is possible to compare the figures of this 10-year group with those of Waite and Beetham as the sclerosis was graded according to their suggested plan.

Graphical comparison may be employed in studying the fundus

changes. (See Graphs 3 and 4.) Realizing that Waite and Beetham's figures are based on cases, more than 60% of which were less than 5 years' duration, the seemingly greater incidence of punctate hemorrhages in the 10-year treated group may be simply a confirmation of a fact prevalent in the literature that hemorrhages tend to increase with duration of diabetes. However, in addition to their findings recorded in Graph 3, in cases of 10 to 15 years' duration, Waite and Beetham have shown that the incidence of deep punctate hemorrhages was 43%, and the average age of the group was 43 years. The incidence of deep retinal hemorrhages in 10-year treated cases was only 31%, and the average age 53 years. It would seem, therefore, that although the therapy used here has not eliminated hemorrhages, it has reduced them. This same analysis can be applied to exudates.



GRAPH 4.—Incidence of waxy exudates.

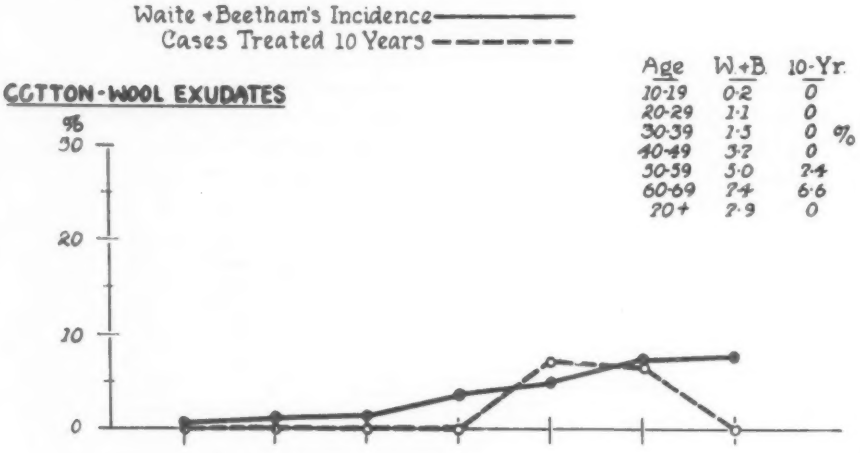
Further findings obtained from this series may be of value in considering the question of specificity of diabetic retinopathy. Analyzing the incidence of punctate hemorrhages according to grade of sclerosis, it is evident that as the sclerosis increases the hemorrhages and exudates increase. (See Table 2.) On the other hand, it is known that arteriosclerosis in the non-diabetic produces less than 5% of punctate hemorrhages at any age, so that arteriosclerosis is not the sole etiologic factor.

There were 20 patients in this series that showed no hypertension, no ECG evidence of myocardial damage, no albumin, casts, or R.B.C. on urinalysis, and no cardiac findings on physical examination. In spite of this, 5 of them, or 25%, showed punctate hemorrhages. Other factors which could be evaluated in this series were:

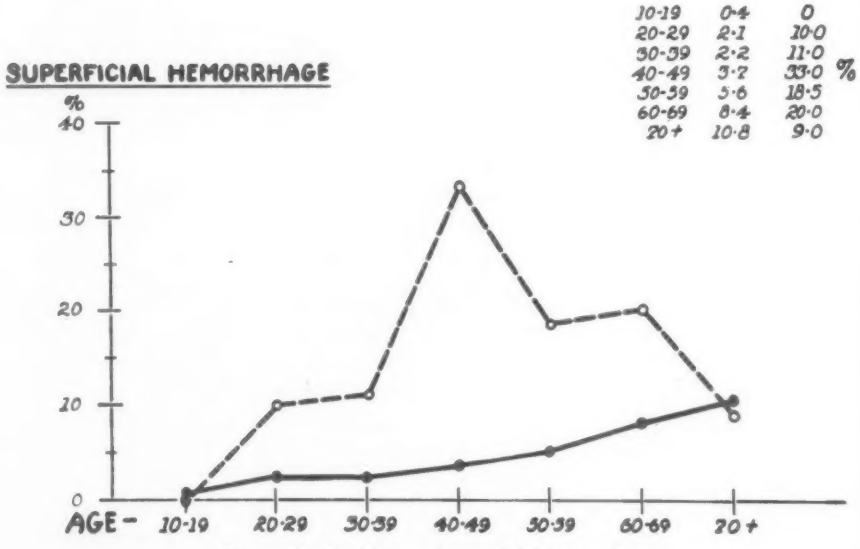
(*a*) Sixteen patients out of 31, or 52%, with blood pressures of above 150 systolic and/or 90 diastolic, failed to show punctate hemorrhages.

(*b*) Ten patients out of 21, or 47%, with evidence of renal damage by albumin or casts or R.B.C. failed to show punctate hemorrhages.

(*c*) Twenty-three patients out of 40, or 57%, showing any form of sepsis ranging from furuncle to tuberculosis, failed to show any punctate hemorrhages.



GRAPH 5.—Incidence of cotton-wool exudates.



GRAPH 6.—Incidence of superficial hemorrhage.

These findings may indicate that, although arteriosclerosis, sepsis, renal damage and hypertension contribute to the production of retinal hemorrhages, they are not the basic etiologic factor.

Of 20 patients showing superficial hemorrhages, all showed at least Grade 2 sclerosis, only 2 showed no evidence of hypertension, renal damage, and had blood sugar levels below 150 mg.%.

According to the accompanying graphic comparison (see Graphs 5 and 6), cotton-wool exudates were similar in incidence to those of Waite and Beetham's, while the superficial hemorrhages showed a greater incidence in the 10-year treated cases.

In this series, there were 3 cases of retinitis proliferans. This is a trifle greater than the incidence in the general population.

No varices were observed in this group; incidence reported by O'Brien and Allen[4] was much less than 1%.

Summary. The following points may be noted:

1. Closely controlled therapy has apparently reduced the incidence of corneal wrinkles in the diabetic.

2. Increased motility of pigment found in the diabetic has not been affected by this form of therapy and there is no significant difference in the incidence in the treated diabetic and in the non-diabetic of iritis, muscle palsies, optic neuritis, optic atrophy, or of the senile type of lens changes.

3. Complicated cataracts are apparently fewer in 10-year treated diabetics than in the untreated.

4. Subcapsular "snow-flake" cataracts are still found in the 10-year treated diabetic.

5. The 10-year treated diabetic has an incidence of sclerosis similar to the non-diabetic and to the diabetic of varying duration and therapy.

6. Deep retinal hemorrhages and exudates increase with the duration of diabetes, and may be slightly decreased by closely observed therapy.

7. Although arteriosclerosis, hypertension, renal disease, sepsis, hyperglycemia, may all influence the incidence of deep punctate hemorrhages and waxy exudates, no one of them is the basic etiologic factor.

8. Increased superficial hemorrhages can be expected with increased duration of diabetes even under closely observed therapy.

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DIABETES MELLITUS AS OBSERVED IN 100 CASES FOR 10 OR MORE YEARS

IV. Peripheral Vascular Findings in 89 of These Cases

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It is well known that patients with diabetes mellitus are predisposed to arterial disease and occlusion in the extremities. Gangrene and amputation have been frequent complications in diabetic patients. As

part of a study carried out by Richardson and Bowie,[8] Edeiken,[2] and Leopold,[5] 89 of their patients who had diabetes mellitus for 10 years or longer were studied to determine the degree of peripheral vascular disease present. These patients were under reasonably good modern treatment, the majority of them from the Diabetic Out-Patient Department of the Hospital of the University of Pennsylvania. They had been on relatively high carbohydrate diets and the degree of control can be seen in Table 3.

Method. A complete history was taken relating to possible symptoms of peripheral vascular disease in the extremities. The patient was questioned regarding pain, coldness, cyanosis, numbness and tingling, edema, phlebitis, cramps in the legs, ulcers and intermittent claudication. The amount of tobacco used was noted.

The physical examination included the blood pressure reading and palpation of the dorsalis pedis, posterior tibial, radial and ulnar pulses. Rapidity of color changes and venous emptying were observed on elevating the legs for 1 minute and then observing the rate of flushing and venous filling when the legs were held in the dependent position. Oscillometric records were obtained at the ankles with a recording oscillometer. The presence of lesions such as ulcers or gangrene was recorded. A reflex vasodilatation test was done where the clinical examination suggested reduction in blood flow. A histamine test was done in a few patients. Roentgen examination for calcification of arteries in the legs was not done.

Evaluation of the degree of arterial occlusive disease present was based on the above studies. Those with actual reduction in blood flow and severe symptoms or lesions were considered severe. Those with reduction in blood flow and with moderate or slight symptoms were considered moderate; those with missing pulses but no reduction in blood flow were considered slight.

Results. Thirty-three of the 89 patients (37%) had evidence of arteriosclerotic occlusive disease (Table 1). In 21 of these the arterial disease was slight, in 9 moderate, and in 3 severe. Five of the 33 were males (15%). Although in the entire group the number of female patients was only 3 times the number of males (67 females [75%], 22 males [25%]), there were more than 5 times as many female patients in the group with peripheral arteriosclerotic disease (28 females [42%], 5 males [22%]). On the other hand, in a representative series of arteriosclerotic patients without diabetes in the Peripheral Vascular Clinic only about one-seventh (14%) were females. The diabetic state, therefore, appears to have played a part in the production of arteriosclerosis, particularly in the female patients of this group.

When one considers the group of 32 patients who were under 50 years of age, there were only 3 (11%) with evidence of arteriosclerosis in the legs; slight in 2, and moderate in 1. In the patients under 50, there was a low incidence of arteriosclerosis not only in the legs but in the heart and eyes (Edeiken[2] and Leopold[5]). This compares with an incidence of arteriosclerosis in 85% of 81 patients under 50 who had been treated by older methods (Rabinowitch).[6] Our own findings in the patients under 50 indicate that premature arteriosclerosis is much less in this series. Rabinowitch[6] reports another group of 28 patients under 50 years who had been treated with high carbohydrate diets in whom arteriosclerosis was found in only 11 or 39%.

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TABLE 1.—ANALYSIS OF PERIPHERAL VASCULAR CHANGES IN PATIENTS WITH DIABETES FOR 10 YEARS OR MORE

Age group (yrs.)	No. of patients	Symptoms of arteriosclerotic peripheral vascular disease in legs				Pulses missing in legs		Oscillometric reading				Grade of arteriosclerotic peripheral vascular disease			
									Reduced						
		None	Slight	Mod.	Severe	One pulse missing	More than one pulse missing	Normal	Slight	Mod.	Severe	None	Slight	Mod.	Severe
10–19	4	4	..	..	..	..	..	..	..	..	..	4			
20–29	10	10	..	..	..	..	2*†	6	3‡	1*	..	7			
30–39	8	8	..	..	..	1	..	6	2	..	..	7	1		
40–49	10	8	2†	..	..	2	2	7	1	2†	..	8	1	1	
50–59	27	21	2	3	1	4	5	14	7	3	3	17	7	2	2
60–69	25	19	1	5	..	1	7	12	7	5	2	13	9	5	
70–79	5	1	1	2	1	..	3	..	2	1	2	..	3	1	1
	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
		71	6	10	2	8	19	45	22	12	7	Total 56	21	9	3
Female	67														
Male	22														
	—														
Total	89														

* Thrombo-angiitis obliterans.
† Arterial spasm in 1 patient.
‡ Arterial spasm in 3 patients.

TABLE 2.—RELATIONSHIP BETWEEN DEGREE OF ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE AND SEVERITY OF DIABETES

Arteriosclerotic peripheral vascular disease		Severity of diabetes in terms of amount of insulin required			
Degree of severity	No. of patients	No insulin	Up to 25 units	Up to 50 units	Above 50 units
None	56	6	18	12	20
Slight	21	7	7	3	4
Moderate	9	1	3	5	
Severe	3	1	2		

Female—67
Male—22

Total—89

TABLE 3.—RELATIONSHIP BETWEEN DEGREE OF ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE AND CONTROL OF DIABETES

Arteriosclerosis		Control of diabetes in terms of average height of blood sugar			
Degree of severity	No. of patients	140 mg. or less	140 to 180 mg.	180 to 250 mg.	Over 250 mg.
Slight	21	4	7	6	4
Moderate	9	1	2	5	1
Severe	3	..	3		
Total	33	5	12	11	5
No arteriosclerosis	56	17	25	15	4

The data in Table 2 indicate that the severity of the diabetes did not affect the degree of arteriosclerosis. The 3 severe vascular cases were all milder diabetics.

The data on the effect of control of the diabetes disclosed a greater percentage with arteriosclerosis who have poor control of the diabetes. In measuring the control of diabetes by the level of blood sugar it should be noted that most of the patients were free of glycosuria. Sixteen (46%) of 35 patients not well controlled (blood sugars over 180 mg.) had peripheral arteriosclerosis, as compared with 18 (33%) of 54 patients who were well controlled (blood sugars under 180 mg.) See Table 3.

Although small necrotic lesions were present in 3 patients, there were no amputations. It is worth noting that this group of 89 patients have had diabetes mellitus for periods ranging from 10 to 25 years without a single patient requiring amputation of a toe or leg. This is at least partly the result of modern emphasis placed on the care of the feet. A great many of the patients had been examined prior to the present study purely to evaluate the peripheral vascular status and to instruct them on the prophylactic care of the feet.

Another finding in the study was the absence of knee or ankle jerks and impaired vibration sense in 31 of the 89 patients. There was evidence of arteriosclerotic occlusion in 24 of these 31 patients. Dry and Hines[1] point out the relationship between lesions of the arterioles and neuritis in the diabetic. They believe that the neuritis is due to involvement of the vasa nervorum.

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Comment. The findings in the group of patients studied, confirm those in other reports[3,4,7] that constant and adequate control of the diabetic with insulin and relatively high carbohydrate diet tends to prevent premature arteriosclerosis. Arteriosclerosis, when it does occur in the well-controlled diabetic, does so at the age when it is also found in non-diabetics. Furthermore, the modern handling of arteriosclerosis in the legs has reduced amputations in diabetic patients. This is due to a number of factors, among which one must mention not only adequate control of the diabetes and prophylactic care of the feet but also the use of sulfonamides. The latter group of drugs has greatly reduced the need for amputating a leg in a diabetic patient because of infection.

The effect of modern treatment on the incidence of arteriosclerosis in the diabetic is not completely evident in the patients past 50. Many of the older patients were on high fat diets at the onset of their disease. Furthermore, many patients do not stay under constant control. A lapse of several months in proper treatment may cause arterial changes which are irreversible (Rabinowitch[7]).

Summary. A group of 89 patients with diabetes mellitus from 10 to 25 years, under reasonably good treatment, were studied from the standpoint of arteriosclerotic occlusive disease in the legs. Three patients (11%) of those under 50 years of age, and 30 (34%) of those over 50 had evidence of peripheral arteriosclerosis.

Premature arteriosclerosis (below 50) was, therefore, not common in this group of patients. The severity of the diabetes did not affect the incidence of arteriosclerosis. The adequately controlled patients had a smaller incidence of arterial disease. Of the females, 42% had arteriosclerotic occlusive disease, as compared with 23% of the males.

There were no amputations in the entire group. Neuritis in the extremities was present in 31 of the 89 patients, chiefly in those with arteriosclerosis.

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Final Summary of Series of 4 Articles. 1. In the 4 preceding papers is presented a study of 100 patients with diabetes mellitus of 10 or more years' duration controlled by insulin and measured diets.

2. Observations show that in at least 45% of them the severity of the diabetes did not progress.

3. Neither the duration nor the severity of the diabetes appears to influence the incidence of hypertension, infection, or ocular sclerosis. However, prolonged diabetes appears to increase the incidence of deep

retinal hemorrhages and exudates and superficial hemorrhages in the eyes.

4. The incidence of cardiac enlargement in those patients who had hypertension is about one-half that observed in non-diabetic hypertensives.

5. In our patients under 50 years of age the incidence of cardiovascular disease was lower than that previously found in diabetics.

6. Arteriosclerotic occlusive disease of the lower extremities was found in 46% of the women examined and in 22% of the men. This much higher incidence in diabetic women than in women without diabetes parallels the greater frequency of coronary vessel disease in diabetic as compared with non-diabetic women.

R. R.

GELATIN AS A PLASMA SUBSTITUTE

THE EFFECT OF GELATIN INFUSION ON THE SUBSEQUENT TYPING AND CROSS-MATCHING OF THE BLOOD, WITH A METHOD OF ELIMINATING THE PHENOMENON OF PSEUDOAGGLUTINATION

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EARLY in the course of studies on gelatin as a plasma substitute, it was observed that the addition of gelatin to blood, either *in vitro* or *in vivo*, causes a definite acceleration in the rate of sedimentation of erythrocytes. This phenomenon is associated with the formation of aggregates of long and short, compact rouleaux, and has been referred to by Ivy[1a] under the term "pseudoagglutination." The phenomenon of hemagglutination of erythrocytes by gelatin was first described by Karsner and Hanzlik[2] in 1920. Ivy and his collaborators[1a] recognized its occurrence in dogs after gelatin infusions and noted that a 10% dextrose solution decreased the amount of pseudoagglutination *in vitro*. We have previously reported on the effects in dogs of pseudoagglutination in relation to prolongation in clotting time and increase in the sedimentation rate.[6] Parkins[5] has shown that there is no change in oxygen saturation of dog erythrocytes after gelatin infusion, in spite of pseudoagglutination. Vogelaar[7] has demonstrated the effects of pseudoagglutination of erythrocytes on the sedimentation rate in man and has shown that addition of glycine to gelatin-blood mixtures alters the pseudoagglutination and prevents the increase in sedimentation rate.

Since gelatin is enjoying increasing use as a plasma substitute in the prevention and treatment of shock, and since many patients receiving gelatin may subsequently require transfusions of whole blood

for correction of anemia, it becomes important to determine whether pseudoagglutination interferes with the accurate performance of blood-typing and cross-matching. Actually, this has not emerged as a problem of any importance in connection with our own clinical studies on the use of gelatin;[3] nor have we observed that pseudoagglutination of erythrocytes in any way limits the tolerance of patients for gelatin. However, a recent statement on gelatin by the Sub-committee on Blood Substitutes of the National Research Council alludes to possible difficulty with the typing of blood of patients after gelatin infusion;[4] therefore, it seemed necessary to obtain further information on this subject. The present report is based on experiments which we believe will serve to clarify the problem.

In Vitro Procedure. Oxalated blood of each of the 4 Landsteiner groups A, B, AB and O was mixed with 4% gelatin solution,* to give concentrations of gelatin in whole blood of 20%, 40%, 60% and 80% respectively. This is equivalent to 0.8 to 3.2 gm. of gelatin per 100 cc. of whole blood. The mixtures of gelatin and whole blood were allowed to stand with frequent mixing for periods ranging from 10 to 30 minutes.

Each of these specimens was then typed, using A, B and O typing sera with saline suspensions of erythrocytes taken from the gelatin-blood mixtures. The reactions were studied under the microscope.

In Vitro Observations. In none of the serum-erythrocyte mixtures was there any difficulty in typing. There was nothing in the way of pseudoagglutination, even in the higher gelatin concentrations, which could be considered to be confusing. The only microscopic evidence of pseudoagglutination was the occasional appearance of compact rouleaux of 4 or 5 cells which were never seen in greater number than 4 to 5 areas per low-power field. None of these could possibly be confused with actual agglutination.

No interference with expected agglutination was encountered. No difference was noted between sparse and dense suspensions of cells.

The typing of blood of all groups was in no way affected by the addition of solutions of either 5% glucose in water or 1% glycine in physiologic saline to the serum-erythrocyte preparations.

In Vivo Procedure. Following single and repeated infusions of 6% gelatin solutions (Knox P-11-20) in quantities of 500 and 1000 cc. per infusion, to a maximum total of 3500 cc. in 4 days, blood grouping, and cross-matching was repeatedly done at varying intervals after gelatin infusion on 10 patients.

Blood samples were drawn over time intervals varying from immediately after to 72 hours after infusion. Several blood samples were taken from patients while gelatin was being administered.

Each sample was typed and cross-matched with from 1 to 3 other blood samples from patients who had not received gelatin. Each serum-erythrocyte mixture was prepared in 3 ways: first with serum and erythrocytes only, second with the addition of 5% glucose in water, and, finally, with the addition of 1% glycine in physiologic saline to the serum-erythrocyte mixture. The latter 2 experimental procedures were done by 2 methods. In the first method, the erythrocytes for grouping and cross-matching were suspended in a solution of 1% sodium citrate in physiologic saline to which had been added an equal volume of either 5% glucose in water or 1% glycine in physiologic

* Gelatin solutions were supplied through the courtesy of Dr. D. Tourtellotte of the Chas. B. Knox Gelatine Co., Johnstown, N. Y.

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saline. In the second method, which we have found to be easier and more satisfactory, the glucose or glycine solution was added to the serum-erythrocyte preparation as illustrated in Figure 1.

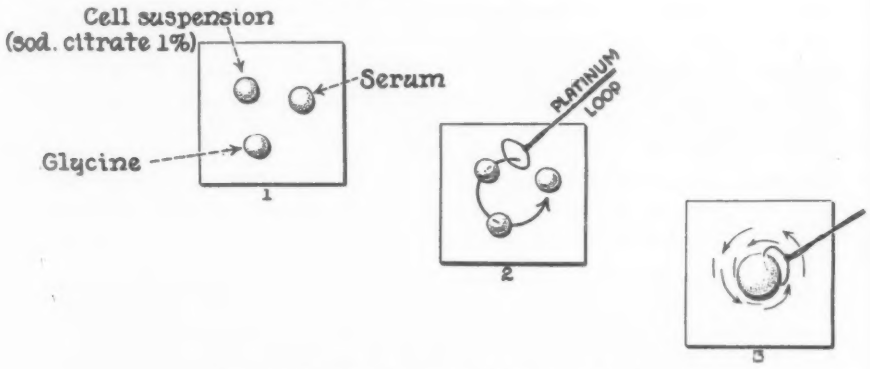

FIG. 1.—Method of cross-matching, using glycine.

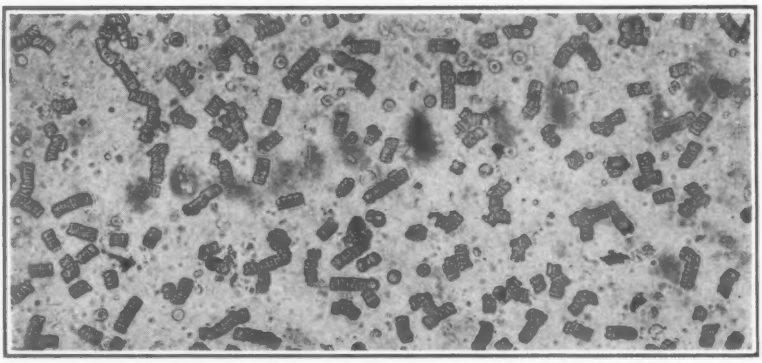

FIG. 2.—Pseudoagglutination 30 minutes after mixture of cells and serum.

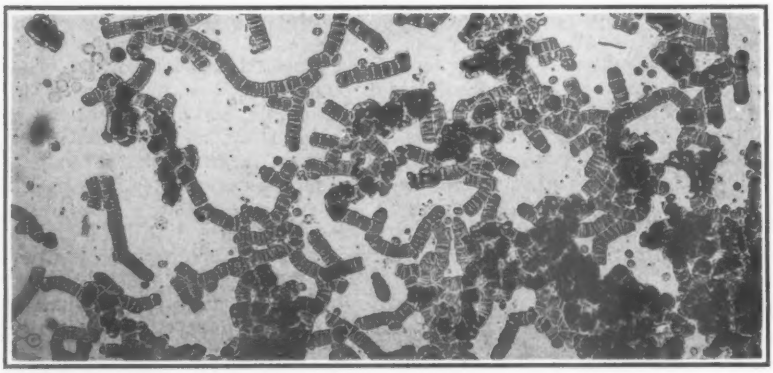

FIG. 3.—Pseudoagglutination 2 hours after mixture of cells and serum.

In Vivo Observations. In the cross-matching of blood of patients who had received gelatin infusions, hereafter called the recipients,

with the blood of normal individuals of the same blood group, hereafter called the donors, the resulting phenomena were uniform.

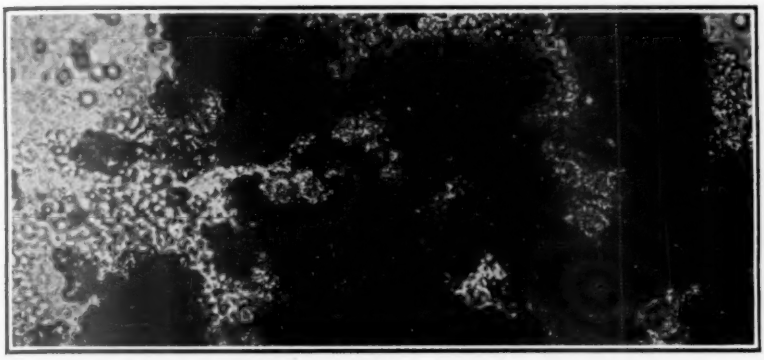

FIG. 4.—Actual agglutination with incompatible cells and serum.

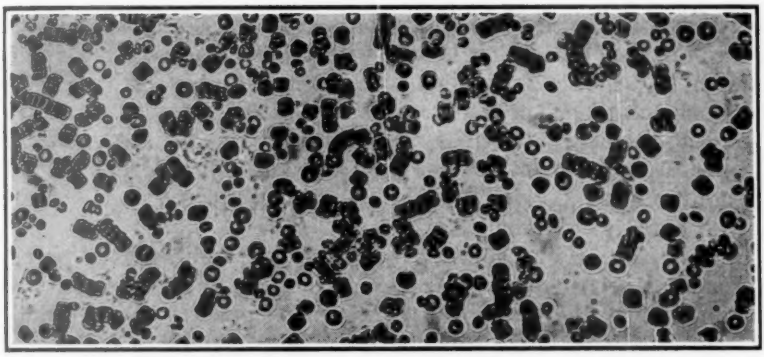

FIG. 5.—Effect of 5% glucose on pseudoagglutination seen in Figure 2.

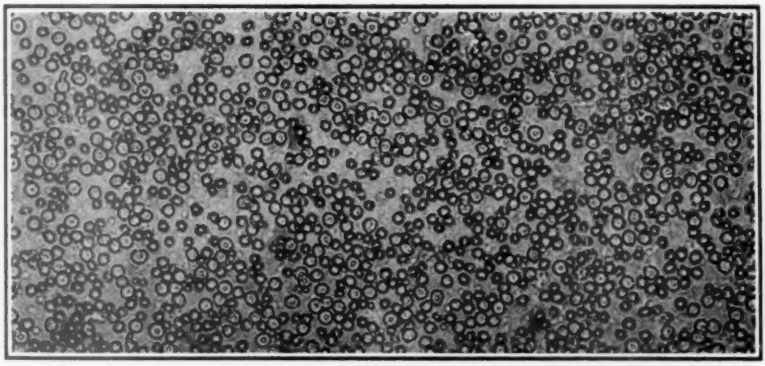

FIG. 6.—Effect of 1% glycine on pseudoagglutination seen in Figure 2.

There was never any abnormal appearance in the suspensions of recipients' cells in donors' sera. The phenomenon of pseudoagglutina-

tion was observed to some degree in all of the suspensions of donors' cells in recipients' sera.

Pseudoagglutination did not always show immediately after mixing recipients' sera and donors' cells. It was usually visible within 10 minutes and most marked in 30 minutes. There seemed to be no relation between the amount of gelatin infused or the time interval after infusion and the amount of pseudoagglutination. In some serum-erythrocyte suspensions there was so little pseudoagglutination that it could be considered a natural variation, and in most the picture was so definitely that of compact rouleaux that even the inexperienced observer would have had no difficulty in differentiating the appearance from that of actual agglutination.

In some of the serum-erythrocyte suspensions, however, there was sufficient pseudoagglutination to be confusing. Figure 2 shows the appearance of marked pseudoagglutination ½ hour after mixture of the cells and serum. Figure 3 represents the end-result after the abnormally long period of 2 hours. Both these photomicrographs were taken from the most marked example of pseudoagglutination we encountered. Figure 4 illustrates for comparison actual agglutination of incompatible blood as it is seen with this technique. Its strikingly different appearance is obvious even when compared with the 2-hour pseudoagglutinated specimen.

The addition of 5% glucose in water to the pseudoagglutinated specimens corrected in part the pseudoagglutination (Figure 5) while the addition of 1% glycine to the pseudoagglutinated specimen abolished it entirely (Figure 6).

In approximately 35 additional patients who had received previous infusions of gelatin varying from 500 to 3000 cc., no difficulty was encountered by the technicians of the blood bank of the Hospital of the University of Pennsylvania in subsequently typing or cross-matching their bloods.[1]

Conclusions. 1. Following the infusion of intravenous gelatin the erythrocytes exhibit pseudoagglutination, characterized by the formation of long and short, compact rouleaux. Even when these rouleaux are in close association their appearance is not that of clumping.

2. The phenomenon of pseudoagglutination in no way interferes with the grouping of blood in patients who had had previous infusions of gelatin.

3. In cross-matching the blood of patients who have received an infusion of gelatin, pseudoagglutination of varying degrees occurs in the normal donors' cells when mixed with such a patients' sera. No such phenomenon is observed in suspensions of patients' cells in donors' sera.

4. Pseudoagglutination of erythrocytes is less marked when a 5% glucose solution in water is added to the erythrocyte-serum suspension.

5. Pseudoagglutination is abolished by the addition of a solution of 1% glycine in physiologic saline to the erythrocyte-serum suspension.

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6. The use of a 1% glycine solution in physiologic saline in no way interferes with the grouping or cross-matching of blood.

7. In spite of the appearance of pseudoagglutination of erythrocytes in blood from patients who have received a previous infusion of gelatin, no practical difficulty has yet been encountered by our technicians in typing or cross-matching such blood.

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DIGILANID AND THE THERAPY OF CONGESTIVE HEART DISEASE*†

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In the past few years two important developments have occurred in the field of digitalis, developments which promise to bring some interesting changes in digitalis therapy. The first of these developments was the adoption by the U.S.P. XII of the cat method as the official assay for digitalis. Thus, after many years of struggle, the cat method of assay was finally officially designated to replace the frog method of assay. The second of these developments, and probably the more important of the two, was the progress in the investigation of the pure glycosides‡ found in digitalis. These investigations seem to indicate that the pure glycosides may eventually replace the crude drug and thus eliminate the need for bio-assay.

While the cat method of assay is superior to the frog method and more closely approximates the values for man, it still has certain flaws which make it desirable to get away from a bio-assay method. Gold *et al.*[4] have shown in a series of studies that even digitalis glycosides with the same toxicity in cats show great differences in potency.

* This study was aided by a grant from the Sandoz Chemical Works, Inc.

† Drs. Frederick Steigmann, Alfred Klein and Richard Martin who were collaborators in the early part of this work are now in the Service. Elizabeth M. Adles helped in the preparation of the statistical data.

‡ The term "glycoside" rather than glucoside is used in this paper according to the suggestion of Arthur C. DeGraff, Bull. Acad. Med., **18**, 246, 1942.

While for a digitoxin type of digitalis the cat units may be taken as a fair guide to potency, great variations occur when using preparations closely related to digoxin or lanatoside C or any other cardio-active glycoside. Differences in absorption and elimination probably account for this fact. This inaccuracy in evaluation of potency becomes particularly important when one deals with digitalis extracts which vary in their glycosidal content according to crop, locality and year. Obviously the ideal solution of this problem will be the introduction of pure glycosides which can be adjusted by weight, thus affording accurate dosage.

With these facts in mind, we undertook to study clinically the therapeutic effect of a mixture of 3 pure crystalline glycosides of Digitalis lanata of known composition. This mixture (digilanid*) was prepared by Stoll and his workers,[6] who found that the composition was constant and the preparation stable, and that when using it the dosage did not vary greatly in obtaining the therapeutic response in the same heart conditions. It was also his observation that, with a knowledge of its strength clinically, the tendency to produce toxic effects is lessened.

Material and Method of Study. Patients with congestive heart disease who entered the Cook County Hospital were used for this study. On entrance into the hospital, all cases of congestive heart failure were divided into two broad classes: (1) emergency, and (2) non-emergency.

In the emergency group, the cases of acute coronary occlusion were identified and eliminated from this study. The cases that were not emergencies were placed on bed rest and sedation for at least 3 days or longer, if the edema was subsiding as judged by the patient's loss of weight. Digilanid was, therefore, not started until it was determined whether the patient was unimproved or worse on bed rest alone.

The daily observations on all patients included:

1. Fluid intake.
2. Urinary output.
3. Weight.
4. Arterial pressure.
5. Heart rate and radial pulse.
6. Daily observations on state of congestive heart failure.

All cases had an electrocardiogram and 2 meter chest Roentgen rays taken on entrance and as frequently thereafter as indicated by their progress. Chest and abdominal aspirations were not done until after the patient had reached a stable weight level except in a few cases that became emergencies.

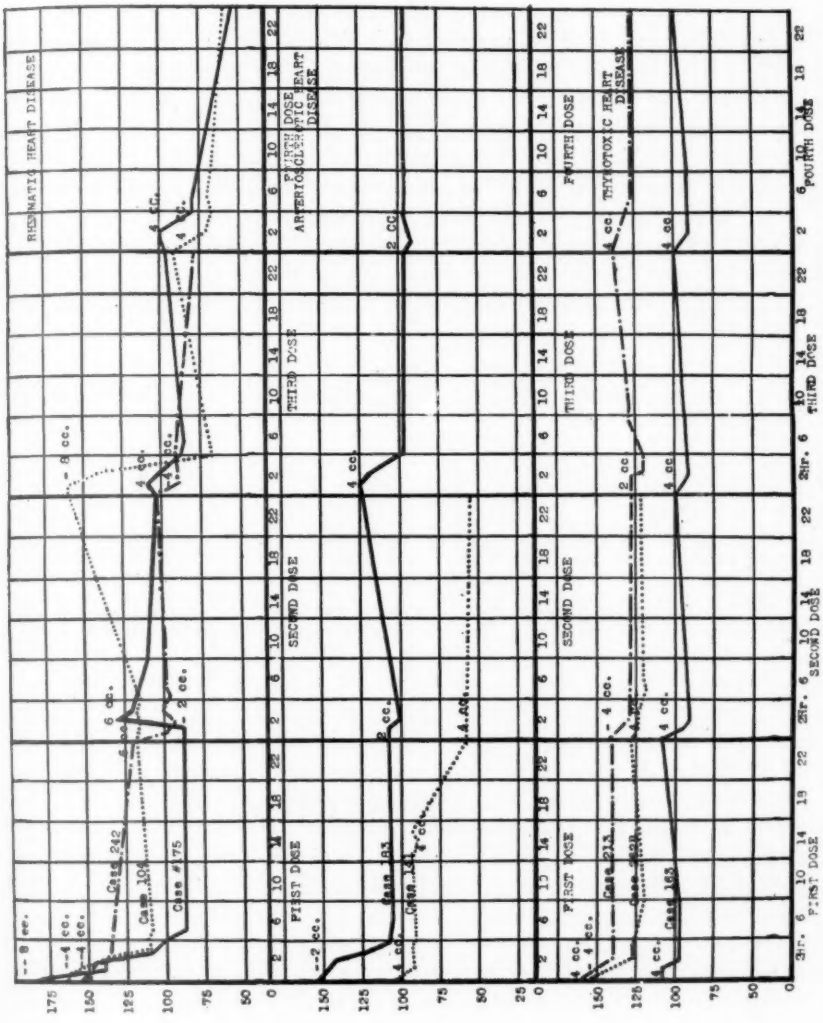
In those cases that still showed edema after weight had leveled off, other therapy was instituted.

Emergency cases were placed at absolute bed rest, given sedation (usually morphine) and 4 cc. of digilanid intravenously or intramuscularly when it was impossible to enter the veins because of the edema. Whenever possible, digilanid orally, 1 tablet 3 times daily, was started also. Additional intravenous digilanid was given only when indicated. It has never been necessary to give more than 2 intravenous injections of 4 cc. on the same day. This method of rapid digitalization was found to be more satisfactory than large doses by mouth, even in those cases that were not emergencies.

In most cases of the non-emergency group, the slow digitalization method was employed by giving 1 tablet of digilanid 3 times daily. These patients received no other therapy except sedation in the form of phenobarbital or

* Digilanid supplied by Sandoz Chemical Works, Inc.

morphine as indicated. They were kept at absolute bed rest except for daily weighing until their weight reached a stable level. If all signs of congestive heart failure had subsided by then, the patient was allowed to get out of bed by easy stages.



GRAPH I

Results. *Intravenous Administration of Digilanid.* In 6 of the 9 cases, good clinical improvement occurred with slowing of heart rate; in 3 cases without much slowing of heart rate. Graph I shows the heart rate of 8 different patients on progressive digitalization with intravenous digilanid. The curves show essentially the action of the intravenous digilanid on the heart rate.

Case 175 illustrates a patient with fibrillation and with a very high heart rate who responded dramatically both objectively and subjec-

TABLE 1a.—EFFECT OF INTRAVENOUS DIGILANID ON HEART RATE

(Maximum Drop in Heart Rate Following Various Doses of Digilanid and Length of Time Required to Secure Maximum Effect)

Case No.	Dose No.	2 cc. dose: Initial heart rate Apical	2 cc. dose: Initial heart rate Peripheral	2 cc. dose: Minimum heart rate Apical	2 cc. dose: Minimum heart rate Peripheral	2 cc. dose: Time to secure (hrs.)	4 cc. dose: Initial heart rate Apical	4 cc. dose: Initial heart rate Peripheral	4 cc. dose: Minimum heart rate Apical	4 cc. dose: Minimum heart rate Peripheral	4 cc. dose: Time to secure (hrs.)	8 cc. dose: Initial heart rate Apical	8 cc. dose: Initial heart rate Peripheral	8 cc. dose: Minimum heart rate Apical	8 cc. dose: Minimum heart rate Peripheral	8 cc. dose: Time to secure (hrs.)
Rheumatic Heart Disease																
175	1	..	..	Increased		..	..	..	..	..	..	190	120	88	84	5
	2	88	84	(excited by												
	3	..	..	another patient)		..	104	92	88	84	4					
	4	..	..			..	96	84	86	86	4					
242	1	..	..	..	..	..	152	140	134	120	2					
	2	..	..	..	..	..	118	102	96	90	4					
	3	..	..	..	..	..	104	100	88	88	2					
104	1	..	..	..	..	..	162	100	100	90	3					
	2	..	..	..	..	..	..	..	..	..	..	160	120	70	68	4
	3	..	..	..	..	..	88	80	68	68	4					
Arteriosclerotic Heart Disease																
183	1	140	140	106	106	4										
	2	106	106	100	100	2										
	3	..	..	..	..	..	124	124	96	96	2					
	4	96	96	92	92	1										
141	1	..	..	..	..	..	88	88	80	80	4					
109	1	..	..	..	..	..	128	128	100	100	3					
	2	..	..	..	..	..	100	100	96	96	2					
	3	109	109	94	94	1										
	4	89	89	80	80	1										
	5	84	84	80	80	1										
	6	80	80	78	78	1										
Thyrotoxic Heart Disease																
163	1	..	..	..	..	..	108	108	96	96	2					
	2	..	..	..	..	..	108	108	92	92	2					
	3	..	..	..	..	..	100	100	92	92	3					
	4	..	..	..	..	..	100	100	92	92	2					
162	1	..	..	..	..	..	150	110	120	88	2					
	2	..	..	..	..	..	128	108	118	88	5					
213	1	..	..	..	..	..	152	130	140	112	2					
	2	..	..	..	..	..	140	140	130	130	1					
	3	..	..	..	..	..	..	..	..	..	..	128	128	120	120	
	4	..	..	..	..	..	136	136	100	100	6					

tively to the administration of 4 cc. of digilanid intravenously, showing a drop of 82 counts in the heart rate within 3 hours. (ECG's showed pulse rates of 190 and 108 respectively.)

One case which did not respond initially was a fibrillator with a heart rate of 104 before administration of digilanid. This case, a hypertensive, 44 years old, entered the hospital with high diastolic pressure and a complaint of severe dyspnea. Only after the second dose was a lessening of the dyspnea apparent.

From Graph I it may also be ascertained that in the larger proportion of cases the administration of 2 cc. did not produce as prompt or sustained an effect, leading to the conclusion that this is not the most effective dose. Likewise 8 cc. can be ascertained to produce a very great drop in heart rate, indicating that this dose is excessive.

While the accompanying tabulation (Table 1) shows only 2 instances in which 8 cc. was administered, these would indicate that the large drop in pulse rate resulting from the digitalis action lasted for a longer period of time.

TABLE 1*b*.—EFFECT OF INTRAVENOUS DIGILANID ON HEART RATE (IN 2 CC., 4 CC. AND 8 CC. DOSES)

Size of dose administered	No. of doses	Average decrease in heart rate (beats per min.)	Average time required for occurrence of major heart rate drop (hrs.)
2 cc.	10	10	1½
4 cc.	23	19	3
8 cc.	2	89	4½

A 4 cc. dose intravenously appeared to be the most effective dose, clinically and therapeutically.

Length of Time Required to Secure Major Effect. A dose of 2 cc. secured relatively little effect in 4 cases out of 5. A dose of 4 cc. secured a heart rate drop in all cases. In 9 instances out of 19 the major effect was accomplished in 2 hours or less; in 16 out of 19 instances the major effect was manifested in 4 hours or less. The intravenously administered digilanid, hence, requires about 3 hours to exert an effect on the pulse and other symptoms. With a dose of 4 cc. the digitalis action was apparent within 2 hours in 18 of the 19 administrations. In the 1 exception, the ultimate digitalis action was satisfactory, as far as ultimate pulse slowing was concerned. The length of time required to secure major heart rate drop is indicated in Table 1.

Graph I also shows that in most cases the dose of digilanid administered maintained the digilanid action throughout the 24 hour period.

Oral Digilanid Administration. Of the 18 patients who were given digilanid orally, all showed more or less clinical improvement within an average of 4 days. One showed improvement the 1st day after digilanid, 2 on the 2nd day, 6 on the 3rd day, 3 on the 4th day, 3 on the 5th day, 2 on the 6th and 1 on the 9th. This improvement was manifested by slowing of the pulse rate, disappearance of pulse deficit, increased urinary output, loss of weight, disappearance of edema, disappearance or decrease of orthopnea, disappearance of dyspnea.

TABLE 2.—RESULTS ON ORAL DIGILANID THERAPY (18 CASES)

Case No.	Age	Sex	Blood pressure: Initial Syst.	Blood pressure: Initial Diast.	Blood pressure: Final Syst.	Blood pressure: Final Diast.	Pulse rate: Initial Apical	Pulse rate: Initial Periph.	Pulse rate: At digitalization Apical	Pulse rate: At digitalization Periph.	Days on digilanid to beginning of pulse drop	No. days required to digitalize patient	Tablets to digitalize (1 tablet: ½ mg.)	Average tablets per day to digitalize	Maintenance dose	Days to edema lost	Pounds of edema lost	Total weight lost	Days in hospital	Clinical improvement
Rheumatic Heart Disease																				
214	50	F	112	90	106	78	132	64	88	N.F.	1	9	34	3.8	1	15	16	22	20	Orthopnea, 60° reduced to 0
195	52	F	135	115	110	80	132	120	80	76	2	6	20	3.3	1	20	50	52	39	Orthopnea, 60° reduced, feels fine
Hypertensive Heart Disease																				
181	63	F	170	110	138	86	120	106	84	N.F.	2	10	26	2.6	1	12	9	10	23	Orthopnea, dyspnea reduced
206	68	F	150	90	164	80	124	N.F.*	96	N.F.	4	18	82	4.0	1	21	27	29	28	
244	56	M	164	98	134	86	92	N.F.	84	N.F.	6	13	39	3.0	?	13	20	20	19	Orthopnea, 90° reduced to 5°
156	30	F	190	140	155	105	90	N.F.	80	N.F.	5	4	12	3.0	1	7	9	10	34	Orthopnea, dyspnea reduced
220	40	F	190	124	190	98	100	N.F.	88	N.F.	9	15	21	1.4	1	21	19	20	27	Orthopnea, 60° reduced to 45°
245	56	M	146	104	126	86	100	N.F.	84	N.F.	5	22	66	3.0	1	17	26	20	30	Orthopnea, 90° reduced to 60°
223	63	F	136	90	120	76	138	N.F.	80	N.F.	4	20	59	3.0	2	12	14	30	29	Orthopnea, 60° reduced to 45°
246	43	M	154	120	124	88	100	N.F.	60	N.F.	3	10	30	3.0	1	14	28	28	16	Orthopnea, 60° reduced to 30°
209	55	F	160	90	160	100	96	N.F.	88	N.F.	3	7	21	3.0	1	14	22	22	16	Orthopnea, 30° reduced to 15°
196	70	F	140	100	125	85	100	N.F.	92	N.F.†	12	?‡	‡	‡	‡	24	12	12	30	
221	51	F	168	118	180	100	88	N.F.	76	N.F.	3	16	46	3.0	1	18	28	28	22	Orthopnea, 45° reduced to 0
228	29	F	190	138	180	100	120	N.F.	100	N.F.	6	18	50	2.9	1	22	11	14	51	Orthopnea, 60° reduced to 15°
Hypertensive Arteriosclerotic Heart Disease																				
172	76	F	160	100	130	70	147	115	105	86	3	17	51	3.0	1	15	28	36	31	Orthopnea, 90° reduced to 0
249	62	M	250	145	212	104	84	N.F.	74	N.F.	4	13	41	3.0	?	13	31	32	24	Orthopnea, 90° reduced to 45°
224	26	F	110	70	110	70	84	N.F.	76	72	2	4	12	3.0	1	4	5	5	14	Orthopnea, 15° not improved
Luetic Heart Disease																				
231	50	F	180	90	..	..	80	N.F.	82	N.F.	No drop	?§	§	§	§	17	19	23	22	Orthopnea, 60° reduced to 0

* N.F.: not fibrillating.
† Final pulse rate, patient not digitalized on discharge from hospital.
‡ Patient not digitalized, received 56 tablets in 14 days.
§ Patient not digitalized, received 41 tablets in 13 days.

Drop in pulse rate became evident within 4 days as an average (in 1 case within 1 day, 3 cases on the 2nd day, 4 cases on the 3rd day, 3 cases on the 4th day, 2 cases on the 5th day, 2 cases on the 6th day, 1 case on the 9th day and 1 case on the 12th day). In 1 case with low initial rate, there was no drop in pulse rate on digilanid, but other evidences of clinical improvement occurred.

Digitalization as shown by slowing of the ventricular rate occurred, on an average, in 13 days, the shortest time being 4 days and the longest 22 days. In 2 days no digitalization occurred.

After reaching a basal weight on bed rest, these patients lost an average of 21 pounds within 15.5 days following digilanid therapy. The maximum weight lost was 50 pounds, the minimum 5 pounds. After the institution of digilanid therapy, 2 patients began to lose weight on the 1st day, 3 on the 2nd, 2 on the 3rd, 6 on the 4th, 2 on the 6th and 2 on the 10th.

Simultaneous with the weight loss there was a loss of edema, which paralleled the weight loss. Synchronous with the loss of weight and edema there was a marked improvement in the respiratory symptoms of these patients, the orthopnea and dyspnea decreased.

The output of urine increased after the first day in 7 cases, after the 3rd day in 3 cases, after the 4th day in 1 case, after the 7th day in 2 cases. There was no increase in the urinary output on digilanid therapy in 2 cases. One of these cases did not show a marked increase in urinary output on bed rest prior to institution of digilanid therapy.

Table 2 shows the number of days required to produce digitalization, loss of edema, the amount of digilanid necessary for digitalization and the amount required to maintain the patient after digitalization occurred.

On oral digilanid, the weight drop usually occurred before the pulse drop. In cases with regular rhythm, subjective improvement, plus weight drop and disappearance of edema, occurred even when there was no appreciable slowing of the pulse.

In the few hyperthyroid cases included in this study, the pulse drop was either insignificant or not as marked as in the other types of heart disease. However, the loss of edema and other signs of subjective improvement were as noticeable as in the others. The hyperthyroid group of heart disease required 2 or 3 times the amount of digilanid for a maintenance dose as did the non-hyperthyroid group. The findings would indicate that while digitalization alone is not sufficient for the treatment of thyrotoxic heart patients, it is a worthwhile adjunct in the therapy of these cases.

From the observation on this group of cases on oral digilanid, there seemed to be no relation between the dose of digilanid necessary for complete digitalization and the weight of the patient, the amount of edema, the presence of liver congestion or the age.

In only 4 of the 18 cases shown in the tabulation (Table 2) did symptoms of overdigitalization appear. In 2 of these instances there were no subjective findings, only signs of it in the ECG of 1 case and in the heart rate of the other. In 2 instances, nausea and vomiting

XUM

occurred; in 1 instance after 23 tablets in 17 days, in the other on the 59th day, 41 days after maintenance dose of 1 tablet t.i.d. had been established.

The oral use of these lanata glycosides seems to result in good therapeutic effect as noted from the pulse drop, loss of weight and edema, and disappearance of dyspnea and orthopnea. Furthermore, since comparatively smaller amounts of this drug can be given than of Digitalis purpurea preparations, there is less possibility of the occurrence of overdigitalization or other side effects.

TABLE 3.—RESULTS OF ATTEMPTED OVERDIGITALIZATION WITH DIGILANID (7 CASES)

Case No.	Dose to secure overdigitalization symptoms: Total amount: Intravenous (mg.)	Dose to secure overdigitalization symptoms: Total amount: Oral (mg.)	Dose to secure overdigitalization symptoms: Average per day (mg.)	No. days administered before overdigitalization occurred	Symptoms of overdigitalization (duration, days): Nausea	Vomiting	Bradycardia	Extrasystoles	Green vision
104	7⅓	2	2⅓	4	3	1	4		
141	2⅔	..	2⅔	1	..	..	6		
175	6	2⅓	8⅓	4	2	1	1		
236	1⅓	10⅓	1	12	..	..	2	12	
117	..	5⅓	0.9	6	..	..	..	3	
217	..	10	2⅔	4	2	1	..	2	
247	..	7⅔	1	8	..	..	..	..	1
Average for group:			2.7	5.5					

Results of Attempted Overdigitalization With Digilanid. An attempt was made to overdigitalize 7 cases by giving them large doses of both intravenous and oral digilanid. The average amount administered was 8 mg.; signs of overdigitalization appeared in an average of 5.5 days on the doses given (see Table 3). The lowest dose to produce overdigitalization was 0.9 mg. average daily dose. This brought on symptoms after 6 days. The highest dose was 2.7 mg. which produced signs of overdigitalization in 1 day. Bradycardia and extrasystoles were the first symptoms to appear and persisted longest, nausea and vomiting occurred in only 2 cases, vomiting persisted only 1 day.

Summary. Digilanid, a complex of lanatosides A, B and C, the pure glycosides of Digitalis lanata, adjusted by weight, was studied in 27 cases of congestive heart failure. Our investigation proves digilanid to be an effective cardio-active preparation, which has the advantages of purity, stability and accuracy as to dosage and therapeutic effect.

The average oral digitalizing dose is 12⅔ mg. (38 tablets) while the oral maintenance dose was found to be ⅓ mg. (1 tablet) in all but 1 case, which required ⅔ mg. (2 tablets).

Digilanid intravenously in doses of 4 cc. (2⅔ mg.) proves to be a potent therapeutic agent in congestive heart diseases with either normal rhythm or auricular fibrillation. The intravenous administration in doses of 4 cc. is particularly indicated in cases of emergency, since its effect is reached within 3 hours, thus saving time of hospitalization.

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AN EPIDEMIC OF PLEURODYNIA WITH PROMINENT NEUROLOGIC SYMPTOMS AND NO DEMONSTRABLE CAUSE

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Since epidemic pleurodynia was first described as a disease entity by Daae[3] in 1872, a number of outbreaks have been reported from Iceland,[6] the Scandinavian countries,[7] Germany,[15] England, and the United States.[4] It is said to be endemic on the island of Bornholm off the coast of Denmark, and in Europe is called Bornholm disease.

The unusual prominence of symptoms referable to the central nervous system constitutes the chief reason for adding to the literature this report of an outbreak of the disease among a group of student nurses. Ordinarily headache, photophobia, myalgia, and hyperesthesia are the only symptoms referable to the nervous system. Sylvest[11] mentions a case of encephalitis noted in one of the Swedish epidemics. Meningo-encephalitis does not, however, appear as a prominent feature of the disease prior to the epidemic reported from Weisen, Germany[9] in 1941. Cooper,[2] in describing coincidental outbreaks of lymphocytic choriomeningitis and epidemic pleurodynia in Cincinnati in 1935, speculated on the relationship of the 2 diseases. De Rudder,[5] in analyzing the epidemiologic data on anterior poliomyelitis and epidemic pleurodynia, was impressed by the similarity of the 2 diseases. He put forth the hypothesis that epidemic pleurodynia is a pathologic variant of poliomyelitis. Wohl[11] attempted bacteriologic confirmation of this hypothesis, but was unsuccessful. Williams[13] has recently reported the occurrence of myalgia most severe in the trapezius muscles but also involving the extremities in 5 English soldiers, appearing a few days after typhoid-paratyphoid immunization. Fever, headache, nuchal rigidity, Kernig's sign and an erythematous skin eruption were also noted. In 2 cases, the spinal fluid pressure was increased with an excess of lymphocytes present. One of these patients developed

pleuritic pain with a small homolateral pleural effusion during the course of the disease. Williams commented on the resemblance of the myalgia in his cases to that seen in epidemic pleurodynia. The most suggestive evidence that the etiologic agent of epidemic pleurodynia may be neurotropic, is found in the report by Howard *et al.*[8] of an epidemic occurring in Brooklyn in the summer of 1942. Among the 161 cases reported, there were 5 instances of meningitis and 3 of meningo-encephalitis. Many of their patients had headache, photophobia, and hyperesthesia of such severe nature as to suggest a central origin.

In its classic form, the onset of the disease is marked by sudden, sharp pain (accompanied by hyperesthesia), usually localized to the epigastrium and referred around the thorax to an area corresponding to the insertion of the diaphragm. This is soon followed by fever, which is accompanied by generalized headache, photophobia, myalgia, and occasionally by nausea and vomiting. The fever is peculiar in that it rises steadily to a peak (usually 102° to 103° F.) within the first 12 hours, and thereafter falls to normal during the next 12 hours. With the rising fever, there is an exacerbation of all symptoms; these subside as the fever falls. Such febrile and symptomatic exacerbations may recur several times before recovery, with intervening remissions of 1 to 2 days' duration, the course of the disease usually running from 5 to 10 days. Complications are rare, the commonest being pleuritis. Otitis media, sinusitis, orchitis, pyelitis, and very rarely, bronchopneumonia and fibrinous pericarditis are mentioned. The prognosis for recovery is excellent, no fatal cases having been reported. Except for some residual weakness, the symptoms usually disappear coincidentally with the subsidence of the last exacerbation. Occasionally cramplike pains in the legs and twinges of pleurodynia may recur for 3 or 4 weeks after defervescence. Since necropsy material has not been available, little is known of the pathology of the disease. Biopsy of the latissimus dorsi muscle in one instance[12] yielded no positive information. Unsuccessful attempts have been made to reproduce the disease experimentally by animal inoculation with pharyngeal washings from patients.[2]

The etiology of epidemic pleurodynia remains obscure. No attempts to isolate the causative organism appear to have been reported prior to 1924. In that year, Small[10] described a plasmodium in the erythrocytes of 2 patients with the disease, but the etiologic importance of this organism was not established. In 1935, unsuccessful attempts were made to recover an organism or virus from blood, spinal fluid, and nasal washing from patients in the Cincinnati epidemic.[2] Unsuccessful attempts were likewise made to identify the causative agent in the cases described in this report (*vide infra*).

The group of 16 cases, here reported, occurred among the student nurses in the Training School of the Hospital of the University of Pennsylvania. The first case appeared August 7, 1943, in a nurse just returned from an affiliate service at the city's communicable disease hospital. No case of the disease was known to have occurred at this

institution either prior or subsequent to its appearance in this patient. Other cases of pleurodynia were observed among the city's general population at this time, so that it might have been introduced into the nursing school by a case outside the institution. Fresh cases continued to appear among the personnel of the Training School at 8 to 14 day intervals for 3 months until November 11, 1943, when the last case was seen. The dates of appearance were: August 7, 22, 31; September 1, 2, 3, 12, 15, 21, 23, 28; October 2, 4, 27; November 11.

The first 2 cases were classical in their symptomatology and course. The onset in each case was marked by nausea and vomiting without prodromal symptoms. Headache, fever, photophobia, and pleurodynia appeared almost immediately. The symptoms subsided coincidentally with the fever only to be followed by several exacerbations at 24 to 36 hour intervals. The disease lasted 10 and 12 days in these 2 patients. It was with the appearance of the 3rd case that affection of the central nervous system by the etiologic agent was first noted. The 3 cases presenting the most striking evidence of involvement of the nervous system are summarized below:

Case Reports. CASE 1. M. C., a 19 year old student nurse, attended the first 2 cases of pleurodynia. Six days after her first known exposure, she complained of an intense, generalized headache. This was her only symptom, and fever of 100.8° F. was her only physical finding on admission. By the following morning she had developed slight nuchal rigidity, a positive Kernig's sign, and photophobia of such severity that not only the shade but the blackout curtain in her room had to be kept drawn to give her relief. A lumbar puncture was done, and perfectly clear fluid under a pressure of 155 mm. of water was obtained. On microscopic examination, the fluid contained 20 cells per 100 cc., all lymphocytes. The protein content was 60 mg. per 100 cc., the sugar 51 mg. per 100 cc. Her initial total leukocyte count was 8700 and never exceeded this level. The differential spread was normal. Both blood and spinal fluid cultures were negative.

The patient's temperature dropped to normal on the 3rd hospital day and rose only once thereafter, reaching 99.4° F. on this occasion. The headache, nuchal rigidity, and photophobia disappeared 3 days later, and she was discharged 10 days after admission. Ten days later, she was readmitted with typical diaphragmatic pain, which was made worse by deep inspiration, headache, nausea, vomiting and fever. The course of the disease was somewhat atypical in that there occurred each evening a rise in temperature to 99.2–.4° F., accompanied by disproportionately severe generalized headache and myalgia. The low grade daily fever with similar symptoms persisting over 2 to 3 weeks was seen in 5 other cases.

CASE 2. Even more striking involvement of the central nervous system is illustrated by the case of Miss D. G., a 21 year old nurse who gave a history of sudden onset of nausea, vomiting, diarrhea, severe headache, and lumbar pain. The headache was the most persistent symptom, and was only temporarily relieved by morphine. The day following admission, she suddenly developed severe bilateral sciatic pain and hyperesthesia manifested by diminished response to pin-prick over the area supplied by the first lumbar and the first and second sacral roots. She preferred to lie flat on her back with her legs flexed on a pillow at an angle of 45 degrees. Straightening the legs or flexing them any more acutely caused severe pain in the lumbar region. In addition to the pain and hyperesthesia, there was marked tenderness to palpation of the muscles of the legs and lower lumbar erector spinæ group. All tendon reflexes remained normal, and no pathologic reflexes could be elicited. Her optic disk margins were hazy, but there was no measurable

papilledema and the fundi were otherwise normal. The spinal fluid was clear, and under a pressure of 150 mm. of water, no cells were found; the protein content was 25 mg. per 100 cc. Except for aortic and mitral murmurs, which had been present prior to this illness, and the hyperesthesia mentioned, the physical examination was negative. The temperature did not rise above 99.4° F. at any time, and only reached this level the first 3 days of her illness. Her symptoms disappeared as dramatically as they had occurred on her 8th hospital day. She was discharged on her 10th day and has remained well since. Pleurodynia was not present at any time, but in view of the patient's close association with typical cases of epidemic pleurodynia, it seemed probable she suffered from an atypical form of the disease. The neurologic consultant who saw this patient as well as several others included in this report, made the following comment: ". . . . if the sensory changes are authentic, they suggest involvement of the spino-thalamic tract of the spinal cord, in addition to meningeal signs. Whenever this agent appears, it seems to have some propensity for invading the nervous system."

CASE 3. At the peak of the epidemic, 1 case occurred with a clinical picture suggestive of encephalitis. The patient was a 20 year old nurse, who had also been in attendance on her ill classmates. After 4 days of severe headache, she became stuporous and remained in this condition for 3 days. During this time she could be roused, and although her mental processes were sluggish. She was well oriented and could answer questions coherently. When not disturbed, she lapsed back into stupor. As she gradually became more wakeful, episodes of unconsciousness were noted. These were characterized by a fall in respiratory rate to a level of 3 to 6 per minute and by loss of consciousness. She could not be roused during these attacks by painful stimuli, but the administration of oxygen appeared to terminate them. At no time did she become cyanotic, although one episode is said to have lasted an hour. The patient was not aware of these attacks and exhibited no aural symptoms. The periods of unconsciousness occurred 2 to 3 times daily for a week, and thereafter decreased in frequency and finally disappeared altogether at the end of 3 months.

Physical examination was negative except for some lumbar tenderness and haziness of the optic disks similar to that seen in several cases of pleurodynia.

Determinations of blood sugar and urea nitrogen, serum calcium and inorganic phosphorus, plasma proteins, chlorides, and carbon dioxide combining power all yielded normal values. Examination of the spinal fluid likewise showed nothing abnormal. Roentgen ray of the skull were negative. An electro-encephalogram made following her initial stupor showed no abnormality. A tracing made during a subsequent period of unconsciousness showed neither an abnormal nor normal sleep rhythm, which suggested that conversion hysteria might be responsible for her lapses into unconsciousness. No further evidence has, however, been obtained to support this diagnosis.

During the 2 months which followed her acute episode, she had 5 similar attacks. She has since remained well.

Comment. Even in the cases which exhibited the typical chest pain and gastro-intestinal symptoms of pleurodynia, irritation of the nervous system was the most striking feature. Because of persistent, boring headache, most of the patients preferred to lie perfectly flat and completely still. Any motion of the head or trunk was said to make the pain unbearable. Morphine, in doses of $\frac{1}{6}$ to $\frac{1}{4}$ grain, gave only transient relief. In only 1 or 2 instances was there relief following the removal of spinal fluid, so that irritation rather than pressure appeared to have been the cause of the headache. Several patients complained of unusual sensitivity to noise and mechanical vibrations, suggesting the possibility of hypothalamic involvement. Haziness of

the optic disk was a common finding during the course of the disease, with a return to normal a week or two after recovery.

TABLE 1.—CLINICAL DATA PERTAINING TO PATIENTS WITH PLEURODYNIA

Patient	Age	Prodromal symptoms	Initial symptoms	Location of pain	Hyperesthesia
1. E. L.	21	None	Headache; pleurodynia	Head; along attachment of diaphragm	In area of pleurodynia
2. L. B.	21	Chill; pharyngitis	Vomiting; pleurodynia; generalized myalgia	Head, back and along diaphragm	About thorax; over flexors of legs
3. M. C.	19	None	Headache; malaise; fever	Head, back, over flexors of legs	In areas of pain
4. M. A. B.	19	Exanthem on arms and trunk 3 days prior to onset	Pleurodynia; headache	Head, back	Generalized
5. R. R.	20	None	Nausea; vomiting; malaise; headache	Along diaphragm, lumbar, sciatic distribution	Corresponding to pleurodynia
6. D. G.	19	None	Nausea; vomiting; diarrhea	Lumbar region; sciatic distribution	Flexors of legs
7. E. T.	19	None	Pleurodynia; headache; malaise	Corresponding to diaphragmatic attachment	In area of pain
8. B. M.	19	Headache for 1 wk.	Stupor	Lumbar area	Corresponding to area of pain
9. M. C.	19	Headache; malaise	Pleurodynia; headache; nausea; vomiting	Generalized abdominal, along diaphragm	Generalized
10. M. A.	19	Cough; pharyngitis	Sore throat; pleurodynia	Along diaphragmatic attachment	In area of pain
11. C. Q.	20	Cough; pharyngitis	Headache; pleurodynia	Along diaphragmatic attachment	In area of pain
12. M. T.	20	Pharyngitis	Pleurodynia; malaise	Prostrating myalgia	Generalized
13. M. E.	18	Rhinitis; sore throat	Pleurodynia; malaise	Along diaphragmatic attachment	Generalized; objected to weight of bedclothes in areas of pain
14. D. S.	20	Malaise for 5 days	Chill, fever, sore throat; nausea; vomiting	Epigastric, over flexors of leg, pleuritic	In areas of pain
15. A. L.	19	None	Headache; pleurodynia	Along diaphragmatic attachment	Transiently in area of pain
16. H. E. B.	19	Malaise for 3 days	Headache; pleurodynia	"Breakbone" type of malaise	Generalized (also objected to weight of covers)

Clinical data pertaining to all the patients studied in the outbreak are shown in Table 1 and Table 2.

The significant features of Tables 1 and 2 may be summarized briefly as follows: Pleurodynia was the commonest initial symptom, occurring in 10 patients.

Mild prodromal symptoms referable to the upper respiratory tract

were noted in 5 patients. One patient presented a mild erythematous skin eruption on the forearms and abdomen 3 days prior to onset.

All patients complained of severe headache and only 4 failed to show epigastric or thoracic pain.

TABLE 2.—FURTHER DATA ON CASES OF PLEURODYNIA

Patient	Meningeal signs and symptoms	Duration of disease (days)	No. of exacerbations	Sequelæ	Significant laboratory data
1. E. L.	Headache	11	3	Headache; pleuritis	Leukopenia; W.B.C. 5000 and below
2. L. B.	Headache; photophobia	16	5	Cramping pains in legs	W.B.C. 7200 to 5000
3. M. C.	Stiff neck; Kernig's sign	10	Daily	None	Spinal fluid findings: 20 cells (lymphocytes), 155 cm. H_2O pressure, culture neg., leukopenia, W.B.C. 4000
4. M. A. B.	Marked hyperesthesia	6	1	None	Initial W.B.C. 10,000; dropped to 5000 2nd day
5. R. R.	Bilateral patellar clonus	22	Daily low grade fever	Cramping pains in legs	Spinal fluid findings: 76 cells (lymphocytes), 150 cm. H_2O pressure, 24.4 mg. protein, culture neg., W.B.C. averaged 8200
6. D. G.	Diminished pain preception over L_1, S_1 and S_2	9	1	None	Spinal fluid findings: 150 cm. H_2O pressure, no cells, culture neg., 30 mg. protein, W.B.C. 8500
7. E. T.	None	7	None	Pains in legs	None
8. B. M.	Encephalitis	22	5	Loss of consciousness on 6 different occasions in 2 months following discharge	Spinal fluid findings: 230 cm. H_2O pressure, no cells, culture negative, 45 mg. protein, W.B.C. dropped from 12,000 to 4000 in 3 days
9. M. C.	Headache; photophobia	10	None	Headache; sl. myalgia	W.B.C. 9000
10. M. A.	None	7	5	None	W.B.C. 9600
11. C. Q.	Headache; photophobia	30	Daily rise to 99.4° F.	Headache and pain in legs for 1 month	W.B.C. 7000 to 5200
12. M. T.	Intense photophobia; headache; hyperesthesia	60	10	Headache; myalgia recurs with every cold	Leukopenia, W.B.C. 5800, 4700 5600
13. M. E.	Headache; photophobia	14	2	None	W.B.C. 7800
14. D. S.	None	7	None	None	W.B.C. 8500
15. A. L.	Headache	15	Daily rise to 99.2° F.	Pleuritic pain and myalgia	W.B.C. 6500
16. H. E. B.	Intense photophobia and headache for 1 week	23	3	None	Spinal fluid findings: 145 cm. H_2O pressure, cells 1 (lymph), 28 mg. protein, culture neg. W.B.C. 5800, neutrophils 80%, lymphocytes 18%, monocytes 2%

Hyperesthesia usually referred to the thorax or legs was seen in 13 cases.

Other evidence of meningeal irritation (photophobia and/or nuchal rigidity) was present in 12 patients.

Kernig's sign was found in 1 patient.

The duration of the disease varied from 7 to 16 days (average about 14).

The number of exacerbations varied from 1 to 10, the usual number being 3.

Nine patients presented sequelæ which included headache, pleuritis, generalized weakness, and myalgia.

The only consistently significant laboratory finding was leukopenia, which was present in 9 cases, and usually developed on the 2nd or 3rd day. The depression in the total leukocyte count usually lasted about 2 weeks. The low total leukocyte count usually lasted about 2 weeks. The total count varied from 3000 to 5000, with a uniform reduction in the differential formula. Leukocytosis was not observed in any case. Blood and spinal fluid cultures were negative.

The literature contains no reference to therapeutic agents or procedures of specific value in epidemic pleurodynia, and for the present only symptomatic and supportive therapy seems possible. The treatment employed in the cases reported here consisted of salicylates, barbiturates, opiates, parenteral fluids, vitamins, and various supportive measures such as strapping the chest, ice caps, and so on. None of these agents was of much benefit. In 2 cases relapse occurred 4 and 5 times and prostration was so severe that pooled adult plasma was given with apparent benefit.

Drs. G. and W. Henle, of the Children's Hospital of Philadelphia, kindly attempted to isolate the causative agent from material obtained from our patients. Blood, spinal fluid, nasal washings, and urine were injected into hamsters, mice, guinea pigs, rabbits and chick embryos. This material was obtained from our patients at various times during their illness; in 2 cases on the day of onset, in 2 on the 2nd day, in 4 on the 10th day, and, in 1, 15 days after recovery. All the animals remained well. Complement-fixation tests, employing antigenic material derived from the influenza virus and that of lymphocytic choriomeningitis, were performed on 8 of our patients with entirely negative results.

Summary. An outbreak of epidemic pleurodynia, affecting 16 young women in a nurses' training school, is described. The source of the epidemic was not determined. Signs and symptoms referable to the central nervous system were unusually prominent. Such neurologic manifestations dominated the clinical picture of 11 patients. In 3 of these patients the symptoms resembled those of meningo-encephalitis, suggesting that the etiologic agent might be neurotropic. Attempts to reproduce the disease in animals were unsuccessful.

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THE RELATIONSHIP OF COLD AGGLUTININS TO THE COURSE OF PRIMARY ATYPICAL PNEUMONIA

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Several investigators have recently discovered that cold (low temperature) agglutinins of varying titer are found in the sera of some patients suffering with primary atypical pneumonia.[5,7] Others have observed complications, such as peripheral vascular thrombosis[2,4] and acute hemolytic reactions,[1] following an attack of this pneumonia. High titers of autohemagglutinins (cold) were implicated in all of these unusual reactions and seemed to be directly responsible.

During the fall months of 1943, a small epidemic of primary atypical pneumonia occurred here and was followed closely in the laboratory, particularly in regard to the changing titer of serum cold agglutinins. One death is reported in this series with interesting pulmonary pathology. Although all of the characteristic cases of atypical pneumonia in this group were found to have high titers of cold agglutinins, a subsequent epidemic showed that this reaction was not consistent. None of the patients with the disease during the winter months developed autohemagglutinins but many were found to have strongly positive Kahn precipitin tests. A later report will deal with this phenomenon.

Criteria for Diagnosis. The symptoms, physical signs and clinical course of the patients with primary atypical pneumonia in this group were identical to those described by Reimann *et al.*[8] and Dingle *et al.*[3] The diagnosis was made after the patient had satisfied the following tests:

1. Symptoms of sore throat, headache, chills and fever, paroxysmal dry cough, substernal pain, generalized aches.
2. Negative lung signs from 4 to 7 days, changing to râles, without consolidation usually in the lower lobes.
3. Chest Roentgen ray[9*] evidence from the 4th to 10th day.
4. Negative sputum examination for pathogenic bacteria.
5. Normal W.B.C. count and differential, or slight leukocytosis.[11]

In this way, 15 patients were found to comply to this critical standard.

Methods. A regimen was worked out so that each patient suspected of developing primary atypical pneumonia had blood withdrawn for cold agglutinins titration every 4th day after the 1st or 2nd hospital day. The day of the disease indicated on the figures was reckoned from the onset of the symptoms.

Cold agglutinin determinations were performed by using serial dilutions of fresh serum (not inactivated)† and adding washed 2% suspension of Group O cells. Fresh suspensions of washed Group O cells were checked against a negative and known positive serum. Readings were made under magnification immediately after removal from overnight icebox incubation. The racks were then allowed to stand at room temperature or warmed in the incubator to insure resolution of the R.B.C.. Invariably, the cells became smooth upon warming to 37° C.

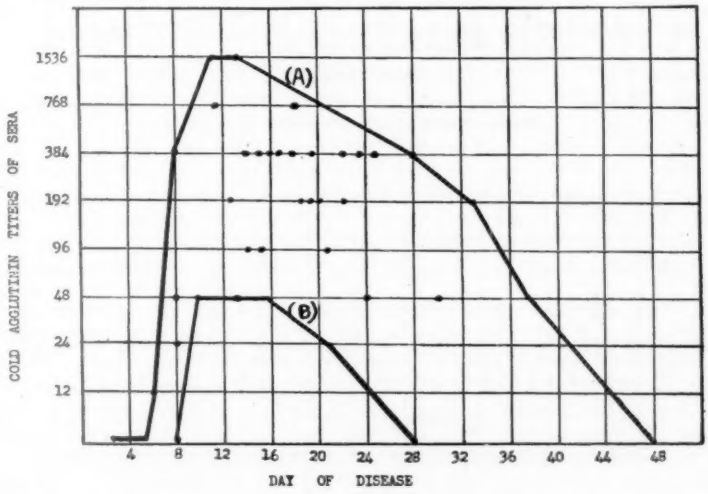

FIG. 1.—Cold agglutinin titer determinations of 15 patients with primary atypical pneumonia; taken during the course of disease.

Results. Figure 1 shows a spot graph of 49 cold agglutinin determinations during the illness of 15 patients with primary atypical pneumonia. The solid top line (*A*) represents the earliest positive test, the highest titer and longest duration of cold agglutinins encountered in these patients. The lower line (*B*) represents latest appear-

* I wish to thank Major George H. Brown, Chief of *X*-ray Service, who read all of the chest films.

† Several positive sera were inactivated and found to give the identical titer of the original serum.

ance, the least titer and the earliest disappearance of cold agglutinins. Highest titers were encountered from 11th to 13th day of illness.

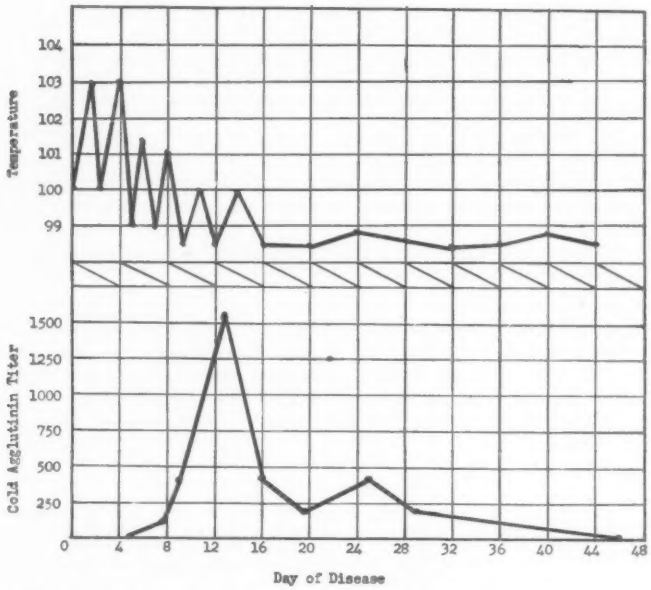

FIG. 2.—Cold agglutinin titer change in the course of illness of the usual patient in this group with primary atypical pneumonia.

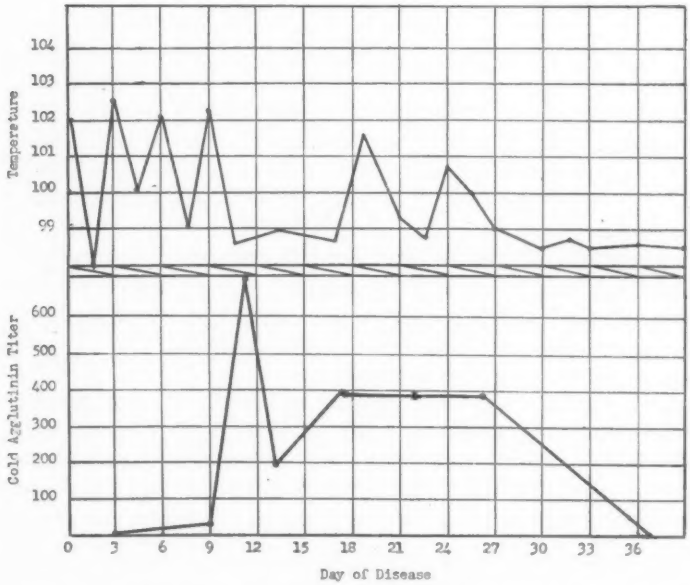

FIG. 3.—Cold agglutinin titer change in one patient with a relapse of fever and symptoms.

Figure 2 illustrates the titer of the cold agglutinin synchronized with the temperature record during the course of a typical case of "virus" pneumonia. The peak of the serum titer is reached on the 13th day as the temperature is on the decline and then its agglutinability decreases sharply, lingers at a lower titer, finally going to zero after a few days of normal temperature. From personal observation, these patients are most uncomfortable at the peak of the cold agglutinins when the paroxysms of cough are difficult to control even with codeine.

Figure 3 is a record of cold agglutinins and temperature and is similar to Figure 2 up to the 15th day when a relapse occurred with increased temperature and spreading lung signs. This is reflected also in the cold agglutinin titer which increased and held a plateau until the temperature finally receded.

Complications. Two patients in the group became seriously ill on the 10th day of their illness, corresponding to the peak of the cold agglutinin titer. Instead of improving steadily with fever by lysis, these patients had emesis of food and water, increasing dyspnea and a remarkable spread of pulmonary signs so that moist râles were clearly audible in all lung fields. This was accompanied by fever rise and leukocytosis.

Case Reports. CASE 1. A soldier was admitted to the Station Hospital on Aug. 16, 1943, complaining of sore throat, cough, fever and headache for 2 days prior to admission. Physical examination revealed only a distinct pharyngitis and W.B.C. equaled 12,000, with differential of 74 neutrophils and 26 lymphocytes. He was started on sulfathiazole but at the end of 3 days, the drug was stopped because the temperature continued to rise to 102 to 103° F. daily, and he had moderate nausea and emesis. However, no physical signs gave a hint as to the cause of the fever and the W.B.C. remained at 11,400 (79% neutrophils, 19 lymphocytes, 1 monocyte and 1 eosinophil). A study of blood smears was negative for malaria and a corrected sedimentation rate was 41. On the 9th day of illness, a Kahn test was reported positive. The patient complained of numbness of his fingers, although examination of the extremities was negative.

On the 10th day, his condition became rapidly worse, with nausea, emesis, dehydration, dyspnea and for the first time moist râles were heard at the left lower lobe. His temperature rose all day and the râles spread rapidly throughout the entire left lung and right middle and lower lobes. Sputum for pneumococcus typing revealed very few organisms and no typing could be obtained. The W.B.C. was now 24,000 (76% neutrophils, 23 lymphocytes and 1 eosinophil). He was placed in an oxygen tent. Fluids and intravenous sulfonamide were given. Catheterization was necessary for the next 3 days as he gradually improved, although his respirations were of Cheyne-Stokes type for 24 hours. A portable chest Roentgen ray was unsatisfactory. During the next 15 days, the patient gradually improved with clearing of the chest findings, a drop in the sedimentation rate, a negative Kahn precipitin test and normal blood counts. In this phase of recovery, a cold agglutinin test was found to be markedly positive both to his own cells and O cells. No signs of a hemolysin were observed.

CASE 2. A soldier was admitted to the Station Hospital complaining of a sore throat, cough with chills and fever although physical examination was negative. Sputum for pneumococcus typing was negative on the 5th day when râles were heard in the lower lobe bilaterally. Sulfathiazole therapy did not alter his course of daily fever rise and continued cough. On the 10th day,

XUM

he became moderately dyspneic after 12 hours of nausea and emesis of food and water. Parenteral fluids were given and oxygen tent atmosphere instituted after stopping sulfathiazole therapy. Within a few hours, the entire lung fields were filled with râles and he expectorated blood-streaked frothy sputum. Despite supportive measures, pulmonary edema increased and he expired 16 hours after the onset of dyspnea. A cold agglutinin titer taken 24 hours before death was positive 1:192.

An autopsy was done immediately. During the dissection, it was noted that no fluid blood escaped and that the vessels and heart contained clotted blood. The lungs presented the important findings. They were heavy, voluminous, and deep purple-red hemorrhagic areas shown through the pleura. On section, fluid exuded freely from the surface which was mottled with distinct hemorrhagic areas the size of a pea and larger areas involving one-third of the lobe. The pulmonary vessels contained blood clots but no organized thrombi were discovered despite the gross pathologic picture, resembling multiple hemorrhagic infarction. Culture from the trachea resulted in the growth of a Group G hemolytic streptococcus which was neither fibrinolytic nor pathogenic for mice. Cut lung sections were sterile.

Microscopically, the bronchi contained neutrophil cells and the mucosa was hyperemic while the alveoli were engorged with red blood cells, large mononuclear cells and fluid. This engorgement was more acute in perivascular areas. All other organs were normal.

Discussion. Autohemagglutinin in significant titers seem to follow the course of primary atypical pneumonia, rising as the fever abates, reaching a peak as chest signs and symptoms are most acute, and receding as the lung clears and temperature returns to normal. This is the usual course of events. However, 1 patient had a relapse of fever and symptoms, whereupon the "cold" agglutinins rose again (Fig. 3), then decreased with recovery.

TABLE 1.—COMPARISON OF AGGLUTINATION OF O CELLS BY POSITIVE SERUM AND PRECIPITATED GLOBULIN FRACTION

	Patient H		
	Serum	Globulin	Control globulin
1:12	+++	++	−
1:24	+++	++	−
1:48	++	+	−
1:96	+	+	−
1:192	+	+	−
1:384	±	+	−
1:768	−	−	−
1:1536	−	−	−
C	−	−	−

Since the cold agglutinin appears 8 to 12 days after the onset of the disease and disappears upon recovery, it suggests an antigen-antibody reaction. It is conceivable that the virus acts as an antigen within the reticulo-endothelial cells, and after an incubation period liberates the globin fraction which produces the cold agglutinin effect. Most antibodies are found in the globulin portion of the serum protein, therefore it seemed probable that this agglutinin would be found there. Positive high-titered cold agglutinin serum was precipitated by 43% saturation of ammonium sulfate, dissolved in saline, reprecipitated, redissolved in saline and then dialyzed repeatedly against cold saline.

XUM

A negative serum was treated the same. The final volume of dialyzed protein was determined to estimate the dilution. Then these solutions were set up in serial dilutions with washed O cells. The rack was allowed to stand overnight in the icebox. Table 1 shows the results.

The globulin fraction was not quite as strong in the low dilution but is of equal titer. This experiment was repeated with other serum and found correct. Therefore, it seems that cold agglutinins are for the most part in the globulin protein fraction.

A most interesting question arises: Of what clinical significance is the high titer of cold agglutinins occurring simultaneously with acute pulmonary edema and death in one instance? This seems to be more than a coincidence, since it occurred twice while each patient was in his 10th day of illness when cold agglutinins were high. The pathological picture seen in the fatal case was strikingly similar to multiple pulmonary infarction with edema but without thrombosis. It seems logical, however, that small groups of agglutinated cells could form in a relatively cold extremity,[10] act as multiple emboli, and cause the pulmonary "infarction" picture. Death may be so rapid that organization of these emboli would not take place. *In vitro*, the separation of warmed cold agglutinated cells takes several moments. Larger masses of these red blood cells may remain compact upon reaching the lung.

Although few studies have been made on the occurrence of the titered cold agglutinins in various diseases, those which are reported indicate low specificity. Stats[10] mentions Raynaud's syndrome, acute and chronic hemolytic anemias, trypanosomiasis, acute bacterial infections, liver cirrhosis, leukemia, pernicious anemia, lymphoblastomas and bland venous thrombosis, as diseases producing cold agglutinins. In order to determine the usefulness of the test in excluding other diseases, a study of sera from lobar pneumonias and bronchopneumonias were compared in titer to primary atypical pneumonia.

TABLE 2.—COMPARISON OF SERA FOR COLD AGGLUTININS IN THREE TYPES OF PNEUMONIA

Disease	No. cases	No. cold agglutinins performed	Negative tests on these days	Positive tests on these days	Titers
Pneumonia:					
Primary atypical . .	15	49	3, 4, 6, 8, 28, 48	6, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 24, 26, 30, 36	Av. above 1:96
Lobar, acute (types known)*		7	8, 7, 6(2), 5, 4, 3	0	0
Broncho (no specific bacterial types) (*a*)	12	24	2, 3, 4, 5, 6, 7, 9(2), 10, 11, 12, 14(3), 16	0	0
(*b*)	6	9	....	4, 5, 6, 7, 8(3), 10, 13	Av. below 1:48
Infectious mononucleosis	5	5	(*a*) 4 serums negative (*b*) Heterophil titers from 112-7168	....	1 positive 1:48

* These patients responded rapidly to sulfonamide therapy and diagnosis was not questioned. In 6 to 8 days they were feeling well with pneumonia resolving completely.

Bronchopneumonia was separated from either primary atypical or lobar pneumonia because it did not conform strictly to either. This disease ran a short course of fever, early, brief, pulmonic signs, negative sputum typing, irregular response to sulfonamides, and occasionally low-titered cold agglutinins. Perhaps these cases represent a mild form of primary atypical pneumonia. Usually the bacterial flora of the sputum was non-hemolytic or viridans streptococci. One serum of five in infectious mononucleosis cases gave a low titer of cold agglutinins. One patient with lymphocytic choriomeningitis gave a serum cold agglutinin titer 1:96 on the 8th day. Serums showing a cold agglutinin titer of 1:48 or above between the 8th to 16th day of an acute pulmonary disease would seem to indicate primary atypical pneumonia.

Landsteiner and Levine,[6] in reference to autoagglutinins, state that "The stronger sera were found to be active when kept in the icebox for months. Weak sera deteriorate in a few days." Fifty-one positive cold agglutinin blood sera were saved without preservative in the icebox to observe the effect of time upon the titer. It was found that the sera maintained their titer for 6 weeks but, upon the 12 week test, all sera had decreased in titer and some dropped to zero. A slight growth appeared in some, but even the clear uncontaminated sera decreased about the same amount.

Summary. Cold agglutinin titers were followed in 15 cases of primary atypical pneumonia. The reaction was negative for 6 days, became positive in 6 to 8 days, reached a peak between the 10th to 14th day, then gradually decreased during convalescence.

High titers of cold agglutinins were observed during the most serious stage of the disease (10 to 14 days). One patient became critically ill and another died in this stage; both had pulmonary edema.

A possible explanation is offered for the coincidence of high agglutinin titer and marked pulmonary edema with hemorrhagic "infarction."

Not all epidemics of primary atypical pneumonia are found to produce serum cold agglutinins. However, repeated cold agglutinin titers are of value in following the course of an acute pulmonary infection to aid in diagnosis and anticipate complications.

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1. ATYPICAL PNEUMONIA*†

BY THE COMMISSION ON ACUTE RESPIRATORY DISEASES‡
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PRIMARY atypical pneumonia is an acute infection of the respiratory tract, presumably transmitted from person to person by contact, droplets or droplet nuclei. Any consideration of the disease as an air-borne infection, however, is subject to certain limitations. Atypical pneumonia may be one disease or it may be several diseases; it may be produced by one agent or by many agents; it may have only one clinical form with involvement of the lungs or it may vary from the mildest of infections of the upper respiratory tract to the most severe and fatal pneumonia; it may spread only by direct and intimate contact with cases and carriers, or it may be air-borne in the truest sense.

But, in spite of this lack of knowledge and this uncertainty, atypical pneumonia is worthy of mention at this symposium because it is by far the most important type of pneumonia in the Army—constituting, in our experience, a high percentage of all forms of pneumonia—and because it serves as a point of reference for investigation of the relatively enormous group of respiratory illnesses of unknown etiology.

What Is Atypical Pneumonia Clinically? Atypical pneumonia usually begins gradually with headache, malaise, fever, and chilliness. The throat may be dry and "scratchy" but the local upper respiratory

* This investigation was supported through the Commission on Acute Respiratory Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army, and by grants from the Commonwealth Fund, the W. K. Kellogg Foundation, the John and Mary R. Markle Foundation, and the International Health Division of the Rockefeller Foundation to the Board for the Investigation and Control of Influenza and Other Epidemic Diseases for the Commission on Acute Respiratory Diseases.

† The 12 papers on air-borne infection which follow in the present and succeeding issue of this journal (6 in each issue) were given at a Symposium on Air-borne Infection before the 45th general meeting of the Society of American Bacteriologists in New York, May 3, 1944. Dr. Alexander Hollaender, of the National Institute of Health, was convener. Clinical features of atypical pneumonia, and features of the epidemiologic behavior of meningitis, mumps, chickenpox, measles, scarlet fever and streptococcal infection complicated by rheumatic fever are given clarifying discussion. Application in several areas of a wholly new method for control of infection, namely mass chemoprophylaxis with sulfonamide drugs, is recorded. The known methods of environmental control of air-borne infection, *i. e.*, ultraviolet irradiation of confined air, the addition to confined air of germicidal vapors, and finally dust-suppressive measures, are each considered, and progress is indicated in the development of equipment and in specifications of design for practical installations. These papers reflect substantial gains toward the development of a practical art of air sanitation since the subject of air-borne infection was last comprehensively reviewed in 1942 in the A. A. A. S. volume on *Aerobiology*.
STUART MUDD, M.D.

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XUM

symptoms—running nose, weeping eyes and sore throat—are usually absent in the early stages. A dry, irritating cough, sometimes paroxysmal in nature, develops soon after onset and may be accompanied by substernal discomfort. Physical examination early in the disease ordinarily reveals little except mild inflammation of the upper respiratory passages.

Up to this point, then, there is little in the history or physical findings to differentiate this illness from "bronchitis" or a severe "chest cold." But if a roentgenogram of the chest is obtained, a pulmonary shadow indicative of infiltration will be seen in the large proportion of the cases. Such a radiographic lesion is the one objective criterion required by most authorities to establish the diagnosis of atypical pneumonia.

As the disease progresses, the cough becomes productive. Physical signs of involvement of the small bronchioles appear in the chest. The majority of the patients are only moderately ill for 3 to 8 days. Convalescence is ordinarily prolonged but uneventful, and recovery is the rule.

The above description characterizes the usual case of atypical pneumonia. Variations in this picture, however, are extreme. Some patients may be sick for weeks, and develop secondary bacterial infections or other complications. Others—perhaps more important to this discussion—may have such a mild illness that they continue to work and the disease is only detected by radiographic examination. Still another group of cases warrants emphasis at this point, since it may provide one of the keys to the solution of the problems of common respiratory disease. The group has been termed "suspected atypical pneumonia" and includes cases like those described above, except for the absence of a pulmonary lesion by roentgenogram. The patients are less severely ill, but physical signs indicate pulmonary involvement. This group of cases seems to lie midway between atypical pneumonia and undifferentiated acute respiratory disease, without sharp border lines between the 3 groups.[6] Undifferentiated acute respiratory disease presents the big problem in respiratory disease, since its incidence is many times greater than that of atypical pneumonia.

What Is Atypical Pneumonia Etiologically? The answer to this question is still unknown. A similar clinical syndrome may be produced by certain bacteria, fungi, rickettsiæ and known viruses. But these well-recognized agents can be excluded with reasonable certainty in the great majority of cases.

The search for new agents has not been neglected. A number of investigators[1,2,3,6,7,8,10,12,13,15] have reported the isolation of viruses from cases of primary atypical pneumonia. These agents have been obtained by inoculation of ferrets and mice, mongooses, chick embryos, cats, cotton rats, guinea pigs and mice, after preliminary growth in tissue culture.[11] Thus far, however, a clear-cut relation between one of the agents and the human disease has not been established.

Two recently described serologic tests—cold agglutinins for human

R.B.C.[9,14] and agglutinins for an indifferent streptococcus[13]—are of some help in diagnosis, but have given thus far no definite clues to the causative agent.

Transmission experiments in human volunteers with throat washings and sputa of patients with atypical pneumonia have been more encouraging.[5] Approximately 7 to 14 days after inoculation by spraying, 10 of 12 volunteers developed acute respiratory disease varying from mild attacks to moderately severe illnesses during which cold hemagglutinins appeared in the sera of 3 cases. This experiment provides some evidence that atypical pneumonia is an air-borne infection.

How Does Atypical Pneumonia Behave Epidemiologically? Since its recognition, atypical pneumonia has shown no specific concentration with respect to race, sex or geographic area. The majority of the cases have been reported in adolescents and young adults, which is probably due to better facilities for recognition in this age group.

Sharp outbreaks have occurred in some of the eastern cities, in preparatory schools, colleges and military installations. Attack rates in certain of these epidemics have been high, varying from 14 to 40%. The incidence in contacts has also been high, and case-to-case spread has been apparent.

In contrast to this picture, however, the ordinary occurrence of atypical pneumonia in the Army is endemic or sporadic. Cases appear in the various organizations as if they were distributed at random, with the single exception of hospital personnel, where the incidence is significantly greater and concentration of cases can be demonstrated.[6] A further interesting, and perhaps significant, correlation has been noted between the incidence of atypical pneumonia and that of acute undifferentiated respiratory diseases.[4] The relationship of one to the other is relatively constant and both show seasonal variations. Both also occur with greater frequency in new recruits than in "seasoned" troops.

How Is Atypical Pneumonia Related to the Problem of Undifferentiated Respiratory Disease and to Air-borne Transmission? The manner of spread of atypical pneumonia will probably not be finally elucidated until the causative agent is isolated and the susceptibility and resistance of the host can be determined. A working hypothesis, however, can be employed, and one has been postulated by a number of investigators from different types of data. It seems reasonable to consider atypical pneumonia as a more severe form, with pulmonary involvement, of undifferentiated acute respiratory disease. In support of this theory are the following observations: (1) The gradation of types of clinical illness. (2) The epidemiologic relationships between atypical pneumonia and other undifferentiated respiratory illness. (3) The production of varying types of respiratory illness in human volunteers.

Proof must await further etiologic studies, but if these relationships hold true, the "disease" now called "atypical pneumonia" may constitute a large part of the problem of respiratory illness.

Thus far, no intermediary vectors, such as food and insects, have

XUM

been incriminated for atypical pneumonia. Contact, droplet and air-borne methods of transmission appear to provide the manner of spread. The only measures of control which appear to be hopeful are those to be discussed in this symposium for preventing air borne transmission. If such measures can be shown to be effective, further information of the true nature of "atypical pneumonia" will undoubtedly be obtained.

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2. FACTORS IN THE CONTROL OF THE SPREAD OF ACUTE RESPIRATORY INFECTIONS WITH REFERENCE TO STREPTOCOCCAL ILLNESS AND ACUTE RHEUMATIC FEVER*

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Rheumatic fever is not an air-borne disease but, since attacks of acute rheumatic fever are preceded by hemolytic streptococcus infec-

* The views represented in this paper are those of the authors and do not necessarily reflect those of the Navy Department.

tions in almost every instance, the factors concerned in the spread of hemolytic streptococci are of equal importance in the epidemiology of rheumatic fever.

In any attempt to evaluate the importance of air-borne spread of respiratory illness or to assess the effectiveness of control measures, it is necessary to consider the whole epidemiologic pattern. Respiratory infection spreads from person to person through the air, but the amount of infection which will develop depends on the immune status of the recipients. If accurate knowledge of this receptiveness to infection after exposure in the given population is lacking, differences in morbidity may be exaggerated or minimized beyond their true weight.

Certain of these important host factors and also environmental differences were studied at the U. S. Naval Training Station at Newport, R. I., in the winter and spring of 1940 and 1941, and are the subject of the present paper.

The acute infections of the upper respiratory tract which are encountered in military populations may be divided broadly into 3 categories:

1. The contagious diseases of viral origin (mumps, measles, German measles, and chickenpox). Here, the diagnosis is easy to establish.

2. Bacterial respiratory diseases (those caused by the hemolytic streptococcus, pneumococcus, diphtheria bacillus, and meningococcus). In 1940 and 1941 at Newport, streptococcus infections were the only important group in this category.

3. Acute respiratory infections presumably of non-bacterial origin (some of these are called coryza, others have the clinical characteristics of atypical pneumonia, and in certain cases, usually in epidemic periods, the virus of influenza A or B is isolated). In the Navy, febrile respiratory infections without distinguishing diagnostic criteria are usually classified under the blanket diagnostic term, "catarrhal fever acute."

Because immunity to catarrhal fever is not the same as protection against scarlet fever or measles, and because streptococcal infection shows different characteristics of spread than non-streptococcal illness, a differentiation of the total respiratory illness into at least the 2 components, streptococcal and non-streptococcal, is necessary in order to study the epidemiologic characteristics of the diseases and the reaction of the population to these infections.

Figure 1 gives the weekly rates at Newport for visits to the dispensary with respiratory complaints, largely colds and coughs, for admissions with a diagnosis of catarrhal fever and for all admissions for streptococcal infections of which the majority were acute tonsillitis and scarlet fever.

The sharp rise of colds and catarrhal fever in December represents a wave of illness which was probably influenza A. At least the virus was isolated from many parts of the country in the epidemic which was nationwide at that time. The fact that the steep rise of catarrhal fever was paralleled by a similar increase of colds to even higher levels, suggests that the virus was widespread at this early phase of the epi-

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demic and that it caused more infections not requiring hospitalization than febrile illness admitted as catarrhal fever acute.

Streptococcal illness assumed a different curve. Here, there was a straight line trend culminating in a peak in late March. Throat cultures for hemolytic streptococci were only started toward the end of the epidemic, so diagnosis throughout most of the period of observation was on a clinical basis. Without laboratory diagnosis such as throat culturing, catarrhal fever has a tendency to change its character under the same name. Probably in the early winter it was a true influenza, but the plateau effect of the catarrhal fever in the late winter months suggests that streptococcal pharyngitis and tonsillitis were here included under the diagnosis of catarrhal fever.

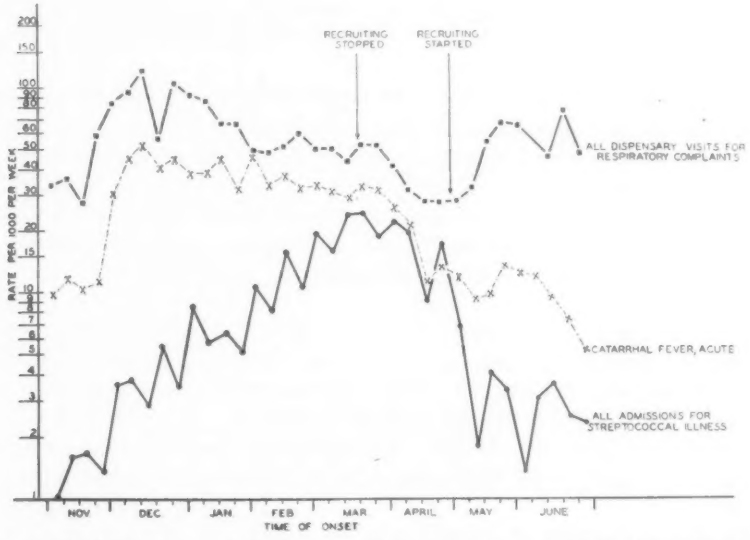

FIG. 1.—Weekly incidence of dispensary visits for respiratory complaints and admissions for streptococcal and non-streptococcal respiratory illness.

Nothing in this chart suggests that the influenza predisposed to secondary invasion by the hemolytic streptococcus. The peaks of the 2 epidemics were 12 or more weeks apart, and with a training period of 7 weeks few recruits were found to have been on the station during both epidemic periods.

Scarlet fever showed such a high incidence in the month of March that recruit reception was suspended for a period of 6 weeks. Following the stopping of recruiting, rates for colds and catarrhal fever dropped off precipitately. A few weeks later, this was followed by a drop in the incidence of streptococcal infection. This serves to emphasize one of the most important determining factors in the genesis of epidemics which is the rate of overturn of the population. It is a verification of the experimental findings of Webster in *S. typhi-murium* epidemics in mouse colonies; that epidemics are a function of the rate

of introduction of susceptibles into an infected herd. Newport had a weekly increment of 400 new recruits into a population of 2500 to 3000 from which an equal number were graduated every week. When this flow of susceptibles was cut off, it was associated with an abrupt decline in the incidence of these diseases.

As a control measure for the curtailing of epidemics, restriction of the flow of recruits should be effective; but this is a heroic measure which would hardly be practicable under present wartime needs of manpower.

The much higher respiratory morbidity in the recruit population than in the permanent personnel living in the same environment can be seen in Figure 2. This is an indication of the relatively greater susceptibility of men entering military camps from civilian life over those of greater Navy age who have undergone the physiologic conditioning and natural immunizations contingent on Naval experiences.

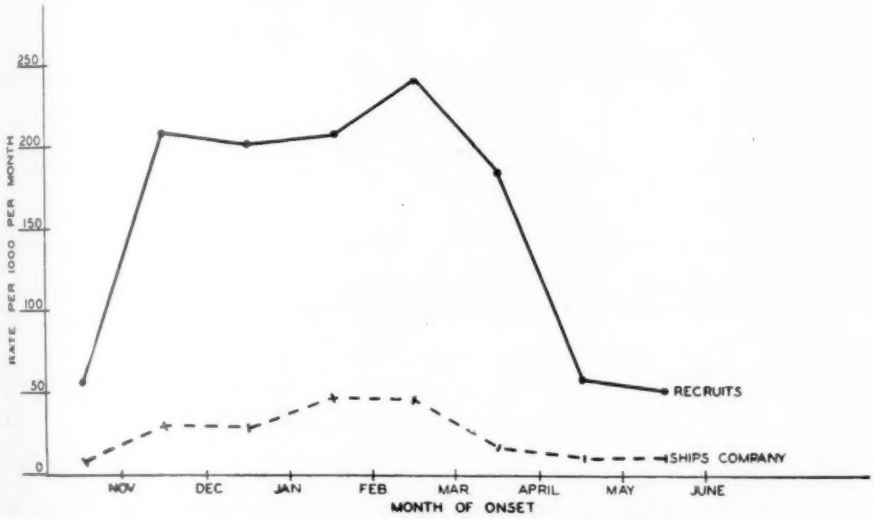

FIG. 2.—Monthly incidence of acute respiratory illness among naval recruits and ship's company (permanent personnel).

Evidence of one specific immunization through exposure was seen by the higher levels of immunity to scarlet fever, as measured by the Dick test in the Ships Company over the recruits while within the recruit population. A 15% reversal of the Dick test was demonstrated after 6 weeks in training during the period of greatest prevalence of streptococci and streptococcal illness.

Illness rates, in terms of Navy age or weeks on station before onset of disease, are shown in Figure 3. Here, the sequence of events would seem to be: a cold in the first 2 weeks, the risk of contracting catarrhal fever rising to a peak at about 4 weeks and falling off symmetrically. Streptococcal infections, apparently, required more time to build up their highest incidence. Perhaps this was due to the necessity of

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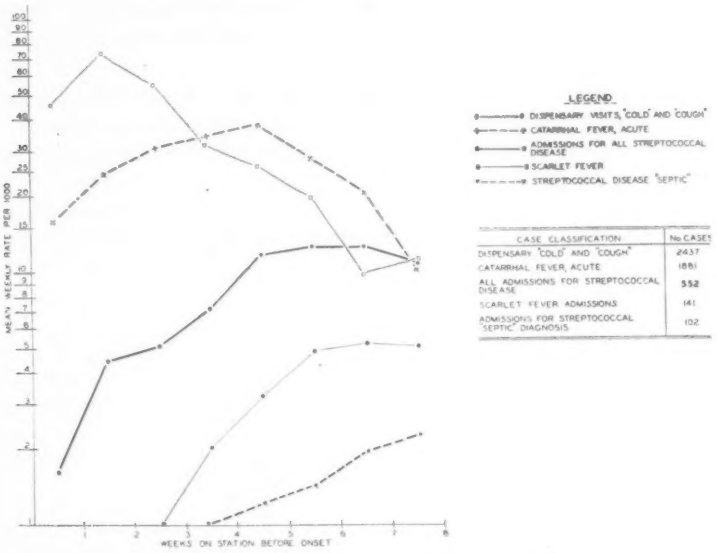
repeated doses and exchange of organisms before effective exposure was established, or perhaps to the predisposing effect of the non-specific respiratory infections, although only a small percentage of the cases represented on these curves are recorded for more than one dispensary visit or hospital admission for respiratory disease.



CASE CLASSIFICATION	No CASES
DISPENSARY "COLD" AND "COUGH"	2437
CATARRHAL FEVER, ACUTE	1881
ALL ADMISSIONS FOR STREPTOCOCCAL DISEASE	552
SCARLET FEVER ADMISSIONS	141
ADMISSIONS FOR STREPTOCOCCAL "SEPTIC" DIAGNOSIS	102

FIG. 3.—Incidence of respiratory infections by number of weeks on station before onset. Rates on basis of population spending given number of weeks in training.

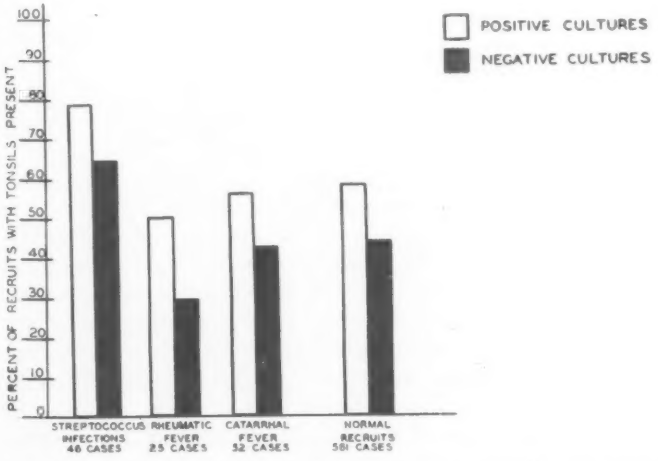


FIG. 4.—Relative percentage incidence of tonsils among recruits with positive and negative throat cultures for hemolytic streptococci in respiratory illness and in the normal population.

The fundamental importance of this factor of time on station or so-called "navy age" can be seen when controlled studies are set up

in such environments to assess various measures for the prevention of air-borne disease. Two groups of recruits alike in all respects, except weeks in training, would show marked differences in morbidity because of this factor alone.

Carrier rates for streptococci have value as an index of the air-borne spread of infection. In the recruit population at Newport, Group A streptococci were prevalent throughout the station at the time of the scarlet fever epidemic and for some weeks following. The Group A carrier rate was 53%, with 65 to 70% of the positive cultures carrying the epidemic strain, Type 6.

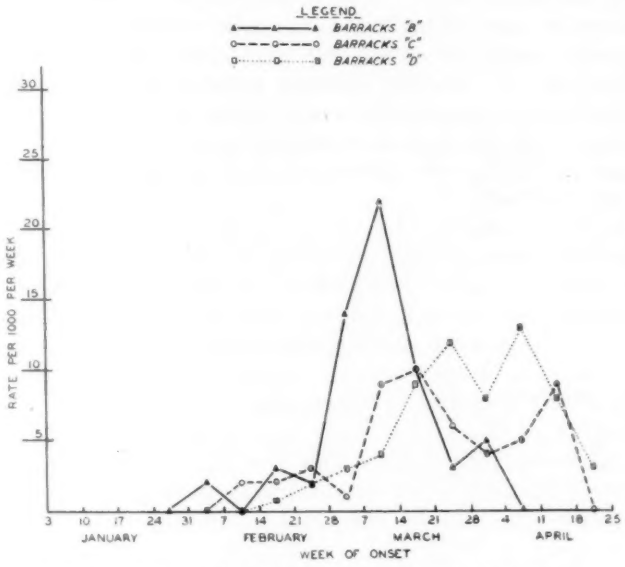


FIG. 5.—Weekly incidence of scarlet fever by barracks

One host factor was found to have an influence on the carrier state, namely, the presence of tonsils. As can be seen in Figure 4, tonsils were associated with the carrier state and also with streptococcal disease. These associations were found to be beyond chance expectation in the group of 700 or more recruits whose illness and culture records were considered in terms of the presence or absence of tonsils.

The contrast of these findings with observations in the childhood age groups might be explained on the change from the lymphoid structure, often with local protective effect in the child, to the cryptic body of fibrous tissue in which is the usual adult tonsil. This latter is probably an excellent lodging place for the hemolytic streptococcus in the adult throat.

The environment of barracks or sleeping quarters was found to have a strong influence on respiratory illness, especially streptococcal infections.

At the time of this study, recruits spent a 3 weeks' detention period in Barracks "D." Following detention the companies were distributed

alternately into Barracks "B" or "C" for 4 weeks further training. Barracks "B" and "C" housing recruits in the same stage of training offered an interesting comparison because of differences in the physical environment. Overcrowding took place to a greater degree and ventilation was much less satisfactory in Barracks "B."

Figure 5 shows the weekly incidence of scarlet fever in each of the 3 barracks. Not only the scarlet fever but all other streptococcal infections without the accompanying rash showed well-defined epidemic features in Barracks "B" which were not so evident in the better ventilated and less crowded "C" barracks.

Bacteriologic sampling of the barracks air was carried out and the importance of poor ventilation and overcrowding in the spread of infection was borne out by highest total colony counts of air samples from Barracks "B" and the frequent isolation of the epidemic strain Group A, Type 6, from the air in this barracks.

Summary. All the factors mentioned seem to fit into 3 attributes mentioned by Dudley in his formula to express the influences controlling respiratory morbidity.

1. The rate of change or overturn of the population.
2. Environmental factors, crowding, ventilation, dust, and so on.
3. Susceptibility of the herd (this is determined by the proportion of susceptibles among new arrivals, age, rural or urban background, and so on). Among those already within the semi-closed military environment, the immune status would depend on recent previous experience with infection on the station.

Obviously, all these factors are not subject to the application of control measures, but a knowledge of their relative importance in the given population allows for a more accurate analysis of the effect of those measures which can be applied.

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3. SCARLET FEVER AS AN AIR-BORNE INFECTION

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The epidemiology of scarlet fever is essentially that of the Group A beta-hemolytic streptococci which cause the disease. The members of this group are divisible into more than 40 serologically distinct types. Practically all strains are capable of inducing local infections in the throat and adjacent structures of the respiratory tract. In addition, some strains are capable of elaborating toxins which produce the rash and other systemic disturbances of scarlet fever. When

Group A streptococci reach the nose and throat of a person with an inadequate antibacterial immunity, local infection of these tissues occurs. If the invading strain of streptococcus is one which does not produce the erythrogenic toxins, the patient will not show the rash and other toxic symptoms of scarlet fever, but will develop what is usually called streptococcic tonsillitis. If, however, the invading streptococcus is capable of toxin production, there are two possibilities. If the host does not possess an adequate titer of antitoxin circulating in his blood, he will, in addition to the localized throat infection, also develop the rash and other toxic manifestations characteristic of scarlet fever. On the other hand, if he does have sufficient antitoxin, no rash will appear and he will undergo an infection which does not differ in any way from that which is caused by the invasion of a Group A streptococcus which does not produce toxin.

The ability of various types and strains of Group A streptococci to spread from one individual to another varies greatly. Some strains spread readily in a population group, while others do not. This variation was illustrated in a study of a group of 400 recruits at the Bainbridge Naval Training Center during January and February, 1944. Table 1 shows that 10% of the newly inducted men harbored Group A streptococci which belonged to 15 different recognized types. During the 6 weeks' training period only 4 types, 1, 17, 18 and 19, spread widely among the men, while the remaining 11 did not.

TABLE 1.—PERCENTAGE OF MEN* CARRYING GROUP A STREPTOCOCCI AT BEGINNING, MIDDLE, AND END OF TRAINING PERIOD†

Type of streptococci	Beginning of training period (%)	Middle of training period (%)	End of training period (%)
1	0.5	5.0	9.8
3	0.3	0.3	0
4	0.3	0	0
5	0.5	0	0
6	0.5	0	0
11	0.5	0	0
17	0.3	3.5	6.8
18	0.5	5.8	10.0
19	4.0	21.3	43.8
22	0.5	0	0
29	0.3	0.5	0.3
30	0	0	0.5
32	0.3	0	0
34	0.3	0	0
35	0	0.3	0
40	0.3	0	0
43	0.3	0	0
44	0	0.3	0
NT‡	1.0	0.5	0.8
Total A	10.0	38.5	61.8

* 400 men comprising 3 companies.
† Training period equals 6 weeks.
‡ Non-typable.

The qualities of a strain of streptococci which determines its dispersability are not known. However, certain factors which influence

this property have been studied. For example, the rate of dispersal of Group A streptococci is greatly influenced by the season of the year. During the summer and fall these organisms do not spread readily from man to man, whereas the spread during the winter and early spring is very great. This is indicated in Figure 1, which shows the percentage of recruits at the Bainbridge Naval Training Center harboring Group A streptococci in their throats during various months of the year beginning in April, 1943. It will be seen that the carrier rate for these organisms was 54% in April, 1943, but that it dropped to 10% during June and to 4% in August, 1943, and remained around 5% until November. It then rose to 10% in December, 18% in January, 1944, and to its peak of 54% in February. A sharp decline again occurred after this to 20% in April, 1944. The monthly incidence of streptococcal respiratory infections corresponded with the carrier rate at each point.

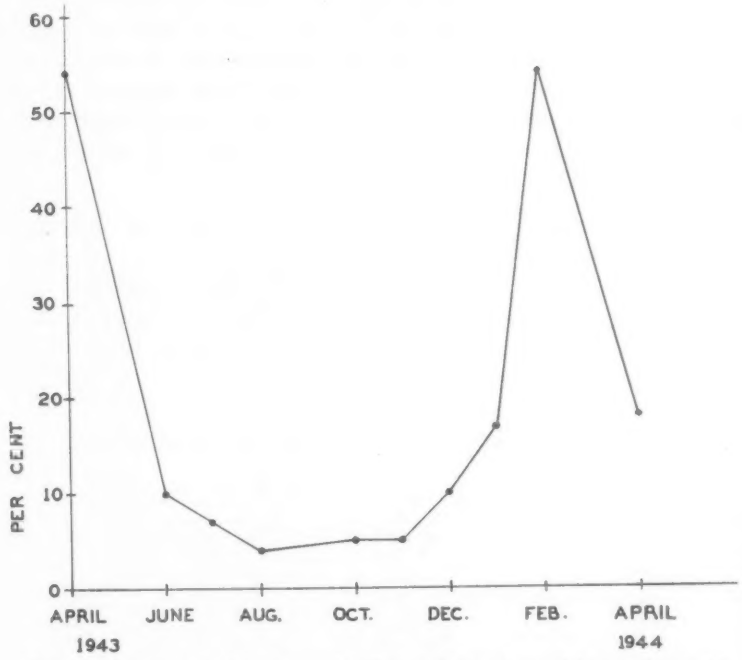

FIG. 1.—Percentage of men carrying Group A Streptococci (average monthly carrier rate)

Since recruits are housed in barracks which offer better opportunity for the spread of streptococci than exists in civilian life, it would be reasonable to expect that the percentage of men harboring these organisms would increase during their stay at the Training Center. As Figure 2 indicates, a rise in the carrier rate actually did occur among men trained during the winter, but no such increase was observed in companies of recruits trained during the early fall. Figure 2

shows the percentage of men carrying Group A streptococci at various stages during their stay at the Bainbridge Naval Training Center. The solid squares represent Group A carrier rates among 400 recruits (3 companies) at various stages during their training period in September and October, 1943. The solid circles represent the rates in 3 companies trained during January and February, 1944. On entrance to the Training Center the carrier rate for Group A streptococci was about 10% in each group. However, the rate rose rapidly among the men in camp during the winter, reaching 38% at the end of 3 weeks and 62% at the end of 6 weeks' stay at the Training Center. On the other hand, the carrier rate among men trained in the fall did not rise during their stay in camp, but remained below 10% throughout the 8 weeks they were under observation.

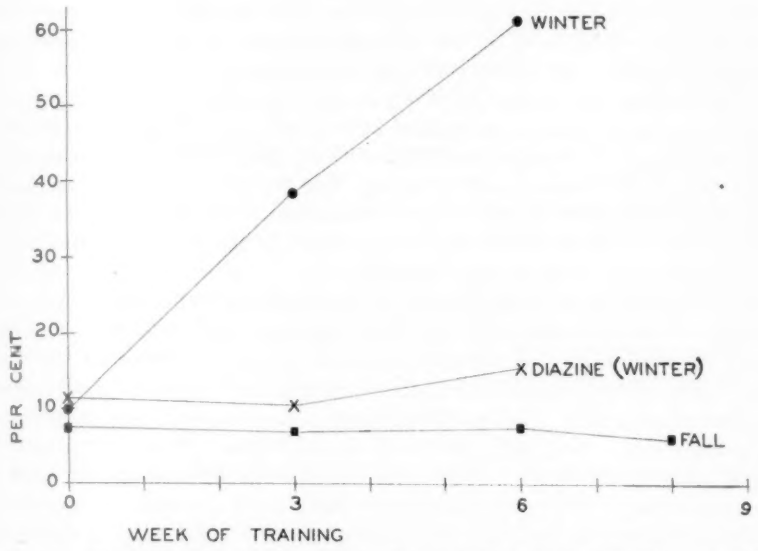

FIG. 2.—Chart showing that the rise in Group A Streptococcic carrier rate which occurs during the training period in winter does not occur during the fall and that it is prevented in winter by sulfadiazine.

The incidence of streptococcal infections in the 2 groups paralleled the Group A streptococcal carrier rate in the 2 groups of men. Thirty-six per cent of the group of men studied during the winter contracted respiratory infections of proven streptococcal etiology. In contrast, the group trained during September and October showed a streptococcal illness rate of only 7% during the 8 weeks they were under study.

It seems clear that Group A streptococci spread much more readily from man to man during the winter than they do in the early autumn, and that a corresponding difference in the incidence of streptococcal respiratory infections probably depends upon this difference in the dispersion rate during the 2 seasons.

The rise in the Group A streptococcal carrier rate which occurs during the winter under normal conditions can be prevented by the daily administration of 1 gm. of sulfadiazine as a prophylactic agent. The crosses on Figure 2 represent the Group A streptococcal carrier rate of 400 recruits who received such medication. There was very little rise in the carrier rate for these organisms during their 6 weeks' stay in camp, although this period extended from the beginning of January to the middle of February, 1944, during which time the carrier rates in control companies reached their peaks. Corresponding with the low carrier rate among men receiving sulfadiazine, a very low streptococcal infection rate was observed.

The mechanism involved in the reduction of the spread of streptococci from man to man by sulfadiazine is not known. The bulk of evidence indicates that the drug is not very efficacious in clearing these organisms from the throat of a carrier. Presumably, streptococci do not become established in the throats of men receiving sulfadiazine so readily as they do under ordinary circumstances.

The mechanical means involved in the spread of Group A streptococci from individual to individual is not well understood. It is known that outbreaks of streptococcal throat infections due to contaminated milk and other foods have occurred, but in the main, streptococcal infections appear to be air-borne. Inhalation of these organisms, with subsequent invasion of the nose and throat of susceptible individuals, is probably the usual mode of spread.

It is known that streptococci are exhaled into the air by normal carriers or by persons suffering from streptococcal respiratory infections. For example, on several occasions we have recovered streptococci on cough plates held at a distance of 2 feet from the mouth of a scarlet fever patient. When this distance was exceeded, no streptococci were recovered. Similarly, we have several times grown streptococci upon blood agar plates exposed for 1 hour at the bedside of scarlet fever patients. We have failed, however, on a number of occasions to recover streptococci from samples of room air taken at a distance of 10 to 15 feet from patients with scarlet fever. Numerous attempts to recover these organisms from the air in a room housing 400 men, many of whom were carriers of Group A streptococci, also yielded negative results. These findings have inclined us to the view that streptococci are not present in large numbers in the general air reservoir, even under conditions most favorable for their dissemination. On the other hand, the evidence indicates that the concentration of these organisms in the immediate vicinity of persons harboring them is quite high. It is probable, therefore, that the chance of infection is greater the nearer a susceptible individual is to a person who is exhaling streptococci. This does not mean that streptococcal infections are not, in the main, air-borne, but that the radius of initial spread may be a relatively limited one due to the fact that these organisms settle rapidly to the floor. Once the streptococci reach the floor they may adhere to particles of dust and again become a hazard at any time that air turbulence causes them to float again. Since streptococci are

resistant to exposure, this process may be repeated many times during the life of the organism. Nevertheless, it is known that dust settles more or less rapidly so that the total period of time the organism is actually air-borne and thus a hazard may not be great. Humidity, the type of dust, the nature of the floor covering, the amount of movement in the room and many other factors influence the rôle of the air reservoir in the dissemination of organisms.

To summarize our views on this matter, we believe that streptococcal respiratory infections are usually air-borne. Infection is most likely to occur in close proximity to a carrier or patient by the inhalation of streptococci from the upper respiratory passages of such individuals. Infection by inhalation of streptococci from the general air reservoir of a room is a definite but probably less important factor in the spread of streptococcal disease of the respiratory tract.

Summary. 1. Most strains of Group A beta hemolytic streptococci are capable of producing disease. They differ widely, however, in their abilities to disseminate in the host population. The amount of illness caused by each strain is proportional to its disseminating ability.

2. Disseminative ability is influenced by climate. It is low in summer and fall and high in winter and spring. It is markedly reduced if sulfadiazine is administered prophylactically to the host group. The mode of action of the drug seems to be to prevent implantation of the streptococci in the respiratory passages.

3. Cross-infection with streptococci occurs by direct air-borne transmission from a carrier or patient to another individual, or less directly by inhalation of streptococci floating in the general reservoir of air. Of these two, the former method is probably the more important.

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4. THE TRANSMISSION AND CONTROL OF MENINGOCOCCAL INFECTIONS*

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The meningococcus can frequently be found in the nasopharynx of apparently normal individuals who, in so far as is known, have not had any contact with clinical meningococcal infections. These persons have been generally called "carriers." Glover has suggested

* These investigations were aided by the Commission on Meningococcal Meningitis, Board for Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Division, Office of the Surgeon General, War Department.

that a "non-contact carrier rate" of 20% or more is a danger signal which presages the occurrence of cases of cerebrospinal fever. However, Dudley and Brennan, among others, have found high "carrier rates" in populations where clinical meningococcal infections were not occurring. Maxcy and Dingle and Finland, in their reviews, have questioned the importance attached to crude carrier percentages. Also, it has not been fully appreciated that the presence of large numbers of nasopharyngeal "carrier" infections during outbreaks of meningococcal meningitis, while required, must be accompanied by other essential conditions. In other words, during periods of unusual prevalence the "high carrier rates" comprise only a necessary but etiologically insufficient condition.

The term "carrier" has many connotations which interfere with a clear understanding of the host parasite relationships. It can be interpreted to imply that the individual may act as a passive vector. It is difficult to concede, however, that living animal tissue can be the site of multiplication of any organism without reacting in some way to its presence. The reaction to such multiplication may be so slight and transient as to escape recognition and be discernible only by an altered response of the host tissue such as antibody formation. It may be so severe as to be obvious to all observers. Reactions in all possible gradations must be considered "infections."

Individuals harboring the meningococcus in their nasopharynx are said by Netter and Debré to exhibit a local reaction to its presence. This observation has not been satisfactorily confirmed. The consensus at present does not accept any distinct specific inflammatory reaction. Whether an antibody response occurs among this group is unknown because the methods available are too crude and complicated. Specific bactericidal activity has been obtained with sera of apparently normal individuals who, to their knowledge, have not had a previous meningococcal infection.

There is no reason to believe that the ecology, with respect to man, of the meningococcus differs from that of *C. diphtheriæ*, *H. influenzæ*, *Streptococcus pyogenes* and others. The classification of "carriers" as infected individuals implies that the clinical syndromes, nasopharyngitis, meningococcemia, or meningitis, are expressions of the degree of invasion rather than any fundamental difference in host parasite relationships. With this concept, cases can be considered uncertain and irregular indicators of the spread of meningococcal infections in a population. The real flow is submerged and can be revealed solely by uncovering subclinical infections.

The Commission on Meningococcal Meningitis arranged an investigation during the spring of 1943 at a large Army camp, (1) to describe the dynamics of subclinical meningococcal infections, according to type, in respect to distribution, prevalence, incidence and duration; and (2) to determine the minimal effective dose of sulfonamides required to obtain parasitic cure of these infections. The size of the samples, the interval between cultures, and the techniques employed were so planned as to furnish valid answers.*

* A detailed report with bibliography appeared in the Am. J. Hyg., 40, 318, 1944.

The results of this investigation disclose several important aspects of the dynamics of subclinical meningococcal infection among Army personnel. The average composite prevalence rate was 40%. Of the 99 men in the group, 92.9% were infected at some time during the study period. Of the 92 positive men, 44 had infections classified as "persistent" under a reasonable definition. An approximately equal number had only "transient" infections. Classification of the plates according to the type and number of meningococcal colonies present did not differentiate between the "persistent" and "transient" infections.

No correlation could be demonstrated between the daily prevalence rates, climatic conditions, the occurrence of upper respiratory diseases and the incidence of the common contagious diseases, including clinical meningococcal infections.

No fixed pattern could be derived from the study of the individual records. Some men were negative throughout the study period. Spontaneous parasitic cures occurred in many. In others, infections with one type would be followed, interrupted, or accompanied by an infection with another type.

The frequency distribution of meningococcal types as isolated from cases was not duplicated when subclinical infections were studied. All the clinical cases at this camp had been associated with the Group I meningococcus. Typing of the strains isolated from cases throughout the Army had shown that 91.6% were Group I. Among the 99 men in control Group "B," 53.5% of the subclinical infections were Group I, 38.4% were Type 2a and 40.4% were Group II.

The high proportion, 92.9% of the 99 men found infected, extended and confirmed the concept that the spread of the meningococcus is primarily at the subclinical level. Only 7 escaped infection during the brief period of 68 days, indicating the extent and rapidity of flow.

It is apparent that the composite or type specific prevalence rate for any given day or for the study period as a whole is a static representation of a biologic equilibrium and does not describe the rate of transmission of the meningococcus. A dynamic process exists and must be illustrated by a dynamic equation. The number of new infections in each succeeding time period, that is, the incidence rate, is a much better index than the level of prevalence attained. If the incidence is increasing, transmission is taking place; if it is decreasing, conditions are operating against the survival of the parasite. The same prevalence may be found in two population groups, yet in one there may be a declining incidence and in the other an increasing transmission of the meningococcus. If all other factors are equal, such as group susceptibility or degree of contact, the latter situation would cause more concern.

With this concept, the hypothesis of a "fixed epidemic level" of subclinical meningococcal infection fails. Glover concluded that there was a correlation between prevalence and the incidence of clinical cases by stating: "A carrier rate of 20% (without awaiting the occurrence of cases) should be regarded as a signal for prompt and effective

action." However, in the development of this thesis, he was actually concerned with the changes in the prevalence rather than the static level. In his report the following inferences were drawn: "A wave of high (non-contact) carrier rates preceded and accompanied an outbreak of cerebrospinal fever . . . there is a carrier epidemic (for the most part entirely devoid of symptoms) preceding and accompanying the much smaller case epidemic." He did not stress sufficiently the importance of this latter observation and later workers have neglected it entirely. From this and other studies of the Commission on Meningococcal Meningitis during the past 2 years, it has been evident that the number of cases would be determined by the incidence of new infections, rather than the prevalence, in any given period.

These observations also offer an explanation of the failure of control measures which have been suggested in the past. The meningococcus must be considered as an "efficient parasite" which maintains itself in any human population through infections at a subclinical level. Only a very small proportion of the total number of infections are followed by clinical manifestations. The latter group acquire the parasite, not necessarily from contact with other cases, but from apparently healthy individuals who have a subclinical infection. As there are no methods for the protection of susceptibles, a reduction in the number of clinical cases can be obtained only by decreasing the probability of exposure to the meningococcus.

Four measures have been commonly employed to interrupt transmission of a pathogen: (1) isolation of the identified infected individual; (2) the treatment of the infected individual; (3) sterilization of the medium of transmission; and (4) protection of the recipient by immunization. The first 2 have failed with the meningococcus because, despite the threshold employed, there is no feasible method of identifying all these suspected foci. For control, the entire population must be considered as the unit and attention directed toward those factors which determine the constants of the biologic equilibrium. It is almost impossible, under the conditions of human intercourse existing today, to change these factors to any appreciable extent. The possibility of reducing transmission by sterilizing the air of enclosed living spaces with aerosols or ultraviolet radiation are still being explored. The lack of any successful immunizing antigen precludes the use of the fourth method. The risk of exposure to the meningococcus can be reduced only if parasitic cure of the infected individuals in a population is obtained without resort to their specific identification.

The sulfonamides have been suggested for the eradication of the meningococcus from the nasopharynx. There are certain administrative difficulties and hazards encountered whenever extensive drug therapy is instituted. It is accepted that some individuals are or will be sensitized to sulfonamides. This usually follows repeated courses. The meningococcus, furthermore, in view of the experience with the gonococcus, may become drug-fast. One of the phases of this study was to determine the optimal dose suitable for mass administration.

The drugs were administered orally under direct supervision.

Group "A" received 1 gm. of sulfadiazine twice daily for 3 days, a total dosage of 6 gm. One and 2 gm. of the same drug were given as a single dose to the men in Groups "C" and "D," respectively. Group "B_1" received a single gram of sulfamerazine.

No toxic reactions, such as rash, fever, urinary complaints, nausea or malaise, were encountered. A few noted dryness of the throat and 2 who had received 6 gm. complained of a mild headache during the course of therapy. No subjective visual disturbances were elicited. Hematologic studies and urinalysis revealed no abnormality attributable to the drugs. However, none of the men had a history of prior ingestion of the sulfonamides.

The criteria selected to assess the efficiency of the chemotherapeutic procedures were: (1) Comparative and absolute reduction of the prevalence level. (2) The length of the resultant negative interval. (3) The frequency of persistence or recurrence of infections with the same type of meningococcus.

The first of these is most easily measured and most apparent. However, the change in the prevalence level does not differentiate between suppression below the threshold of identification and eradication of the meningococcus from the nasopharynx. For this characterization, the last two indices must be employed. For their determination, the same groups must be cultured regularly for a definite period of time. They are influenced by other factors such as the incidence of meningococcal infections in the untreated group and the degree of reëxposure of the treated men. Therefore, these two criteria cannot be used for the evaluation of different studies even though the technical methods are similar.

In this trial, parasitic cure was obtained with 2 or more gm. of sulfadiazine. The 1-gm. doses of sulfadiazine or sulfamerazine were followed by parasitic cure in some and only suppression in others. This conclusion was based upon the following observations: (1) Immediately subsequent to the administration of 2 or more gm. to the 154 men in Groups "A" and "D," all the 85 known prior infections became negative. Only 1 positive result was obtained in an individual who had been negative on 4 previous occasions. When 1 gm. was given to the 103 men in Groups "C" and "B_1," 5 of the 61 prior infections persisted through the first post-drug culture. (2) The reduction in the average prevalence level of Groups "A" and "D" when compared to the results of the concomitantly cultured control group exceeded 85% for the post-drug period. This reduction in Groups "C" and "B_1" averaged about 60%. (3) Comparison of the average prevalence level before and after drug in Groups "A" and "D" revealed a reduction of over 80%, while that for the other groups was approximately 60%. (4) The length of the resultant negative interval when all types of meningococci were considered was 14 days for Groups "A" and "D" and 6 to 8 days for Groups "C" and "B_1." Calculation of this interval with respect to the recurrence of the same type or the occurrence of new infections as manifested by change of type, revealed no material differences. (5) The maximum incidence of recurrent infections with

the same type of meningococcus in Groups "A" and "D" was 6.9% and 14.8%, respectively. In contrast, the incidence of recurrence was 43.2% for Group "C" and 38.2% for Group "B_1."

The use of the sulfonamides, therefore, offers a feasible method for rapidly decreasing the prevalence of meningococcal infections in any limited group. Increasing the amount of drug given as a single dose or repeating the dosage would merely extend the period of meningococcidal activity, provided an adequate level were attained or maintained.

Prophylaxis by chemotherapy, however, cannot control the incidence of reinfections indefinitely. It must be recognized that only immediate parasitic cure or suppression is obtained. There may be a brief refractory period following the administration of the drug, due possibly to a change in the nasopharyngeal bacterial flora. However, there are no grounds, either theoretical or experimental, for the assumption that the sulfonamides, except during the relatively brief period of their activity, confer freedom from, or enhance resistance to, subsequent infection over any long period of time. The rapidity with which the treated groups will attain the prevalence level of the general community will depend upon their degree of reëxposure. Exposure is a resultant of the *effective contact rate* between the treated and untreated groups and the *incidence*, as contrasted to the *prevalence*, of meningococcal infection, among the latter. Any plan for prophylaxis by chemotherapy must consider these factors, and not be determined arbitrarily.

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5. THE CONTROL OF MENINGOCOCCAL MENINGITIS BY MASS CHEMOPROPHYLAXIS WITH SULFADIAZINE*

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The proven efficacy of sulfadiazine in clearing the nasopharynx of meningococci[1,4] has suggested the possibility of controlling meningococcal meningitis in military and naval activities by mass chemoprophylaxis using this drug. The work of Kuhns and his collaborators[3] has proven this to be practicable. The present attempt to control upper respiratory infections at naval training centers by means of sulfadiazine prophylaxis has given an opportunity for evaluating the efficacy of this measure as applied to a large group of men supposedly exposed to meningococcal infections.

Approximately 600,000 men stationed at 8 training centers in the continental United States were given 0.5 gm. to 1 gm. of sulfadiazine daily during their period of training, which averaged 7 weeks in

* This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the author, and are not to be considered as reflecting the policies of the Navy Department.

length. The majority of men received the larger dose. Somewhat smaller but otherwise roughly comparable groups at the same training centers did not receive the drug and served as controls. The total number of man-exposure days in the treated groups was considerably greater than that of the control groups. Since the rates of meningococcal meningitis for the 2 groups are not available at this time, only the actual number of cases for each are given in Table 1.

TABLE 1.—CASES OF MENINGOCOCCAL MENINGITIS IN SULFADIAZINE FIELD TRIAL UP TO JUNE 1, 1944

Activity No.	Period of observation	Treated group cases	Control group cases	Total cases
1	Nov. 5, 1943–June 1, 1944	0	1	1
2	Nov. 27, 1943–June 1, 1944	1*	47	48
3	Dec. 1, 1943–June 1, 1944	0	70	70
4	Dec. 1, 1943–June 1, 1944	0	15	15
5	Dec. 5, 1943–June 1, 1944	2†	7	9
6	Feb. 1, 1944–June 1, 1944	2*	1	3
7	Feb. 8, 1944–June 1, 1944	0	1	1
8	Feb. 18, 1944–June 1, 1944	0	4	4
Total:		5	146	151

* These cases developed within the first 24 hours of chemoprophylaxis.
† These cases were receiving 0.5 gm. of sulfadiazine o.d.

It appeared that sulfadiazine in daily doses of 1 gm. was effective in reducing the morbidity of meningococcal meningitis to practically *nil*. Unfavorable reactions to the drug occurred in less than 0.3% of the treated group. The final morbidity figures and the details of the drug reactions observed are to be included in the complete report which is to be published shortly.[2]

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6. MUMPS AND CHICKENPOX AS AIR-BORNE DISEASES

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Mumps. Experimental evidence on the possibility of mumps being an air-borne disease is limited. Mumps virus has been isolated from the saliva of patients up to 48 hours after onset of the parotitis.[4] Monkeys cannot be infected by merely spraying the nose and throat with virus, but must be inoculated directly into Stenson's duct.[6]

An attempt to infect experimentally a group of susceptible humans[5] required repeated spraying of the throat and the placing of virus-soaked pledgets of cotton in the mouth to bring down 6 out of 13 so exposed—evidence either of low virulence of virus or of relatively low level of susceptibility.

Clinically there are no symptoms in mumps such as coughing or sneezing which would induce any large amount of droplet nuclei formation.

Epidemiologic evidence shows that mumps usually does not occur in epidemics except in aggregations of large numbers of susceptibles as in schools or military groups. The epidemics are not of the static explosive type but tend to continue throughout a whole season.[7] Many are exposed a number of times before developing the disease.[7] It is not at all unusual for siblings with intimate and prolonged exposure to a case of mumps in the household to escape infection. It has been noted that mumps occurring at the same time as upper respiratory infections tends to spread more rapidly and more widely than ordinarily because of the increased droplet formation due to the concomitant sneezing and coughing.[11]

In contagious disease hospitals where opportunity for direct or intimate contact is reduced, the secondary attack rate in susceptibles exposed to mumps is almost *nil* as compared to measles or chickenpox, where the rates are quite high.[14]

Further evidence of the relatively low degree of contagiousness in mumps, provided inapparent infections can be ruled out, is the fact that the age of peak incidence is between 8 and 9 years—the latest for any of the communicable diseases of childhood, and even at the age of twenty years, 40% of the population give a negative history of mumps.[8]

Experimental research with mumps as an air-borne disease is not practical, since monkeys are the only susceptible animal and even these can be infected only by direct inoculation. However, from the standpoint of clinical investigation recent work has provided means of determining the immunity status of exposed individuals other than by the history. A complement-fixation test and a skin test give promise of offering means of determining susceptibility to mumps.[2]

The control of mumps in civilian populations offers little difficulty. With a low mortality rate and relatively rare epidemic outbreaks, it is more of a nuisance than a problem. However, in military populations especially during mobilization, mumps can assume an important place in the causes of disability.[10] From the standpoint of man-days lost in World War I due to disease, mumps was second only to influenza.[9] The high incidence of complications, especially orchitis, adds greatly to the problem when mumps is encountered in military groups. There is evidence already that mumps represents a definite medical problem in the present war.[7]

The use of ultraviolet light irradiation as a means of controlling the spread of mumps in school children has been studied by Wells, Wells and Wilder.[15] Although they conclude that there was less spread in

irradiated as compared to non-irradiated classes, the results are not clear-cut.

On the experimental, clinical and epidemiologic evidence it is concluded that under most circumstances mumps is not a true air-borne disease.

Chickenpox. There is little experimental evidence one way or another as to the air-borne nature of the spread of chickenpox. Virus has been isolated from the local lesions and from the blood and humans have been infected by the intravenous and subcutaneous routes.[12,13]

Clinically, there are few respiratory symptoms, but lesions do occur on the mucous membranes of the mouth and throat; and the apparent respiratory spread of this disease probably depends on this, and on the fact that the virus circulates in the blood and could be thus eliminated through the respiratory mucosa even before the development of lesions. Actually, a chickenpox patient is infectious as long as 4 days before and up to 5 days after the rash appears.[14]

The history of chickenpox shows many epidemic outbreaks. These epidemics are usually of the static explosive type when the disease is introduced into an aggregation of susceptibles. Often just one mass exposure for but a brief period of time results in 100% of the susceptibles coming down with the disease.[11] There have been instances reported of cross-infection with chickenpox in hospitals by the introduction of a susceptible child into a room previously occupied by a patient with the disease. In contagious disease hospitals where the possibility of spread by contact is minimal due to isolation, cubicle technique and aseptic nursing, the pattern of spread of chickenpox is often no different from that in a comparable group of susceptible children not so protected against contact.[3]

The highly contagious nature of chickenpox is evident in the fact that by 10 years of age over 50% of all children have had the disease, and the age of peak incidence is 4 years.[11]

At the present time there are no adequate means of studying chickenpox as an air-borne disease from the experimental standpoint. Animal susceptibility has not been thoroughly investigated, and in humans there is no method of determining the immunity of an exposed individual except by history or the presence of typical scars.

Control of the spread of chickenpox is difficult, due to the fact that the patient is infectious before a diagnosis can be made, the secondary attack rates are high and at present there is no practical means of active immunization. In spite of the low case fatality rate and the relative mildness of the disease, the inconveniences to individuals and to the management of schools and institutions during a chickenpox outbreak make its control desirable.

Several reports are available as to the use of ultraviolet light in the prevention of spread of chickenpox. Wells, Wells and Wilder[15] have reported a marked lowering of the secondary attack rates in irradiated classrooms as compared to non-irradiated using mass irradiation. Others using curtains of ultraviolet light about hospital cubicles have had encouraging results.[3,8]

Chiefly on the basis of its epidemiology it is concluded that chickenpox is probably a true air-borne disease.

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INADEQUATE ACTION OF PENATIN AGAINST BRUCELLA ABORTUS IN VIVO*

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Part I

Culture filtrates of *Penicillium notatum*, designated as "penatin" (penicillin B,[5] notatin[1]) have been shown[1 2] to have a marked antagonistic action against *Brucella abortus* in vitro.

* Financial support for these studies was received from the Pennsylvania Department of Agriculture, United States Bureau of Animal Industry, and the T. H. Dougherty, Jr. Fund.

Method. In order to study the activity as well as any toxic effects of penatin *in vivo* 40 guinea pigs were used. All the animals were tested and found negative to the agglutinative test for brucellosis, and then were each injected intraperitoneally with approximately 1,000,000 *Br. abortus* cells. The strain was the third anaërobic transfer of *Br. abortus* isolated from the milk of a naturally infected cow. The weights of the 40 guinea pigs before infection ranged between 400 and 560 gm., and they were weighed weekly following infection. On the same occasions the weights of 10 non-infected, untreated guinea pigs were ascertained in order to compare the changes in weight of the variously treated infected groups with those of a group of normal animals.

Dosage. The penatin was prepared in separate small batches by the Kaolin method[3] without dialysis. The activity of the different lots varied between 200 and 2000 units* per mg., and since different batches were mixed for injection purposes, an average unit value was adopted, namely, 1000 units per mg. which is the unit value used to express dosages in this report. Different quantities of penatin were used on groups of guinea pigs, and the animals were treated once a day, each dose being suspended in 0.85% NaCl. All injections were made by the subcutaneous route.

Twenty-four hours after infection, administration of penatin was begun on the first group of 10 guinea pigs. Three guinea pigs were injected daily with 10,000 units of penatin for 5 successive days, 5 guinea pigs were injected daily with 50,000 units for 5 successive days, and the remaining 2 guinea pigs were given a single dose of 250,000 units. One week after infection, another group of 10 guinea pigs was subjected to penatin treatment. In this instance, 3 animals were injected daily with 20,000 units of penatin for 5 successive days, 5 animals with 50,000 units daily for 5 successive days, and the remaining 2 guinea pigs received a single dose of 500,000 units. The other 20 infected guinea pigs were left untreated to serve as controls. (One control guinea pig died of intercurrent disease 2 weeks after infection.) During treatment the temperatures of the guinea pigs were recorded before the injection of penatin and again several hours later.

Toxicity. The local toxic effects following the administration of penatin were manifested by swellings which appeared soon at the sites of injection, and which were proportionate to the quantity of the substance introduced. The guinea pigs which received 10,000 units of penatin did not show any local reactions; the guinea pigs injected with 20,000 units of penatin exhibited slight swellings, and those injected with doses of 50,000 units had considerable edematous swellings which persisted for several days, and in some instances caused sloughing of the skin. The introduction of single doses of 250,000 units and 500,000 units of penatin, on the other hand, resulted in marked edema in the subcutaneous tissue with sloughing and rupture of the skin due to pressure. However, the affected areas healed within a week to 10 days without showing signs of infection, although the open wounds were exposed to the air and to rubbing against the bottom of the cages. In addition to the local reactions, there was usually a temporary rise in body temperature following injections of the larger doses of penatin.

Agglutinative Tests and Cultures. Four weeks after infection with *Br. abortus* the guinea pigs were tested for the presence of agglutinins against Brucella antigen. The agglutinative titers ranged from 1:320 to 1:1280, and there was no appreciable difference in the agglutinin

* One unit is the smallest quantity of penatin which will suppress the growth of *Staphylococcus aureus* in 10 ml. of tryptose agar.

content of the blood sera of the treated animals as compared with the untreated controls. Two weeks later (*i. e.*, 6 weeks after infection) 8 guinea pigs from the variously treated groups and 8 controls were killed, and the liver, spleen, kidney and inguinal lymph gland were cultured for the presence of *Br. abortus*. The agglutinative titers determined on blood samples obtained immediately before sacrificing the 16 animals were on a whole similar to the previous titers. Eight weeks after infection, blood from the remaining guinea pigs was obtained for agglutinative tests, the results of which showed in general a slight increase in the concentration of agglutinins as compared to the previous titers of the same animals. One week later, 9 weeks after infection with *Br. abortus*, all the guinea pigs were killed and their tissues cultured for the presence of *Br. abortus*.

TABLE 1.—EFFECT OF PENATIN THERAPY ON BRUCELLA ABORTUS INFECTION IN GUINEA PIGS

Guinea pig No.	Daily dosage penatin in units	No. daily doses	Treatment begun	Total quantity penatin injected in units	Average increase in weight per animal		Culture findings
					4 wks. after infection	9 wks. after infection	
1142	10,000	5		50,000			* Negative
1143	10,000	5		50,000			† Positive
1144	10,000	5		50,000			† "
1145	50,000	5		250,000			* "
1146	50,000	5	24 hours	250,000			* Negative
1147	50,000	5	after	250,000	75.0 gm.	112.5 gm.	† Positive
1148	50,000	5	infection	250,000			† "
1150	50,000	5		250,000			† "
1151	250,000	1		250,000			* "
1152	250,000	1		250,000			† "
1154	20,000	5		100,000			* Positive
1155	20,000	5		100,000			‡ Negative
1156	20,000	5		100,000			† Positive
1157	50,000	5		250,000			* "
1158	50,000	5	1 week	250,000	57.2 gm.	129.0 gm.	* "
1159	50,000	5	after	250,000			† "
1160	50,000	5	infection	250,000			† "
1161	50,000	5		250,000			† "
1162	500,000	1		500,000			* "
1163	500,000	1		500,000			† "
19 infected control guinea pigs: 8 autopsied 6 weeks after infection 11 autopsied 9 weeks after infection					42.6 gm.	68.3 gm.	19 Positive
10 non-infected, untreated guinea pigs					129 gm.	221 gm.	

* Autopsied 6 weeks after infection.
† Autopsied 9 weeks after infection.
‡ Guinea pig No. 1155 died 4 weeks after infection due to cardiac puncture for the purpose of obtaining blood.

The accompanying table indicates the dosage of penatin, the changes in the body weights of the animals following infection, and the results

of cultures of the various tissues at autopsy. The most obvious beneficial effects of the penatin therapy was observed in the general well-being of the treated animals as manifested in the gain in body weight. After the administration of penatin was discontinued the animals gained considerably in weight, and 9 weeks after infection with *Br. abortus* the average increase in weight of the treated animals was almost twice as great as that of the infected controls. On the other hand, the infected, treated guinea pigs showed only about one-half the increase in weight as compared with the group of non-infected, untreated animals. Three of the treated guniea pigs did not yield *Br. abortus* on cultures of tissues at autopsy. One of these (No. 1155) died 4 weeks after infection due to injury of the heart while obtaining blood, and the other 2 animals (Nos. 1142 and 1146) were killed 6 weeks after infection. In addition, a 4th animal (No. 1144) showed only 1 Brucella colony on the liver culture and none in the other tissues. All the controls were positive on cultures. In guinea pigs Nos. 1142, 1144, and 1146, treatment was begun 24 hours after infection, and in guinea pig No. 1155 1 week after infection.

Summary of Part I. Subcutaneous administration of various quantities of penatin to guinea pigs resulted in local reactions in the form of edematous swellings at the site of injection, which were in general proportionate to the quantity of the material introduced. However, a single injection of as high as 500,000 units of penatin did not have fatal effects. Of 20 guinea pigs infected with approximately 1,000,000 virulent CO_2 sensitive *Br. abortus* cells, and treated with penatin, 3 did not yield *Br. abortus* on cultures at autopsy, while all the control guinea pigs were positive. In 2 of the negative guinea pigs, treatment was begun 24 hours after infection, and in the 3rd one not until 1 week after infection. The agglutinative titers of the different animals varied, but there was no distinct difference between the treated and untreated groups. The guinea pigs treated with penatin showed an average increase in weight per animal which was about twice the gain in weight of the non-treated controls.

PART II

On the basis of results reported in Part I it was decided to repeat the experiment, using different doses of penatin on groups of guinea pigs for longer periods of time.

Method. For that purpose, 80 guinea pigs were injected intraperitoneally with about 80,000 CO_2-sensitive *Br. abortus*, and 24 hours later subcutaneous administration of penatin was begun in 40 of the infected animals which were divided into 4 groups.

Dosage. The penatin employed was prepared according to Doisy's[4] U-acetate method, and it assayed 20,000 units* per mg. It was planned to treat the guinea pigs as follows:

Group 1—10 G. P. to receive 160,000 units of penatin daily, divided into 2 equal doses.
Group 2—10 G. P. to receive 80,000 units of penatin daily, divided into 2 equal doses.
Group 3—10 G. P. to receive 20,000 units of penatin daily, divided into 2 equal doses.
Group 4—10 G. P. to receive 2000 units of penatin daily, divided into 2 equal doses.

* One unit is the smallest quantity of penatin which will suppress the growth of *Staphylococcus aureus* in 10 ml. of tryptose agar.

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Each dose of the material was suspended in 2 ml. of 0.85% NaCl, and the injections were made subcutaneously at 9 A.M. and 5 P.M.

The remaining 40 guinea pigs were intended as controls.

Toxicity. Three animals of Group 1 died after the second injection, and 3 other animals after the third injection of penatin, at which time treatment of this group was discontinued. Within the next 48 hours 3 more animals died, and the last guinea pig of Group 1 died 9 days after treatment was stopped. One non-infected guinea pig was injected intraperitoneally with 80,000 units of penatin twice daily, and this animal died after the 3rd injection. Thus it would appear that intraperitoneal injections of penatin are as toxic as subcutaneous ones.

In Group 2, 7 animals died after the 4th injection of penatin (*i. e.*, after each animal had received a total of 160,000 units of penatin) at which time the administration of penatin to the remaining 3 guinea pigs was discontinued. One of these died 48 hours later, and 2 of the animals survived.

The noticeable toxic effects of penatin in the animals of Groups 1 and 2 were: marked edematous swellings in the subcutaneous tissue at the sites of injection, and a moderate rise in body temperature following the injections. However, the body temperature dropped to several degrees below normal several hours before death. The 2 guinea pigs of Group 2 which survived had extensive edematous swellings in the subcutaneous tissue of the ventral thoracic and abdominal region (sites of injections). The skin covering this area eventually ruptured, but complete healing of the affected tissues took place within 3 to 4 weeks.

The guinea pigs in Group 3, which were injected with 10,000 units of penatin twice daily, occasionally showed local toxic effects in the form of edematous swellings which usually disappeared within 24 to 48 hours. Sometimes there was also observed a slight rise in body temperature within 2 hours after injection of penatin, but the temperature returned to normal in a few hours. Only one animal of this group died in the course of treatment, but death in this instance could not be attributed to toxic effects of the penatin. The other 9 animals were treated for 30 days.

The animals in Group 4, which were injected with 1000 units of penatin twice daily, did not show any ill effects from the treatment, and all 10 guinea pigs were treated for 30 days.

Seventy-two hours after infection, when most of the animals in the first 2 groups had died, treatment was begun on 16 more guinea pigs from the control group. Eight of these (Group 5) were injected daily with 2000 units of penatin divided into 2 equal doses, and the other 8 animals (Group 6) received 400 units of penatin daily divided into 2 equal doses. No undesirable effects were noticed from the injections of these small quantities of penatin. The last 2 groups of guinea pigs received penatin injections during the same period as Groups 3 and 4,

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and therefore were treated for 28 days. Thus the full course of treatment was carried out on:

Group 3 with 10,000 units twice daily for 30 days = total 600,000 units of penatin
Group 4 with 1000 units twice daily for 30 days = total 60,000 units of penatin
Group 5 with 1000 units twice daily for 28 days = total 56,000 units of penatin
Group 6 with 200 units twice daily for 28 days = total 11,200 units

Agglutinative Tests. The guinea pigs were tested 28 days after infection with *Br. abortus* for the presence of agglutinins against Brucella antigen. The agglutinative titers ranged from 1:25 to 1:200, and there was no appreciable difference in the agglutinin content of the blood sera of the treated animals as compared with the untreated controls. (All the animals had been tested and found negative to the agglutinative test for brucellosis prior to infection.)

Changes in Body Weights of the Animals. The weights of the guinea pigs before infection ranged between 300 and 450 gm., and they were weighed weekly following infection. On the same occasions the weights of 20 non-infected, untreated guinea pigs were ascertained in order to compare the changes in weight of the variously treated infected groups with those of a group of normal animals. Since the animals of Groups 1 and 2 died soon after treatment was begun, changes in their weights could not be observed. The following table presents the average increases in weight per animal in the remaining groups:

TABLE 2.—AVERAGE INCREASE IN WEIGHT (GM.) PER ANIMAL

	Weeks after infection			
	1	2	3	4
Group 3	10.0	26.0	38.0	74.4
Group 4	41.2	63.0	93.9	140.8
Group 5	38.6	60.0	98.8	148.0
Group 6	32.1	63.8	92.3	134.0
Infected untreated G. P. 24	42.2	61.8	97.6	153.0
Non-infected untreated G. P.	32.4	72.4	95.5	145.0

The recorded figures indicate clearly that the guinea pigs in Group 3 averaged a gain in weight which amounted only to less than one-half the increase in weight observed in the other groups. The animals of this group received the largest non-lethal doses of penatin, and it was noticed throughout the experiment that their food intake was less than that of the animals in the other groups. The general toxic effects of the penatin (fever) and the pain associated with occasional swellings at the sites of injection must be considered responsible for the anorexia. The remaining groups of guinea pigs showed approximately equal increases in body weight.

Cultures of Tissues at Autopsy. All guinea pigs which died before the termination of the penatin therapy were autopsied and their tissues cultured for the presence of *Br. abortus*. Twenty-two animals died during that period, *i. e.*, all guinea pigs of Group 1 and 8 guinea pigs of Group 2 succumbed to the toxic effects of penatin, while 1 guinea pig of Group 3 and 3 non-treated animals died due to intercurrent disease. Most of these animals died during the night, and because of

the warm weather conditions their tissues were decomposed. In those instances, therefore, the culture plates were covered with contaminants and no Brucella could be isolated from the tissues. However, in 5 animals which were autopsied soon after death, namely 4 guinea pigs of Group 1 and 1 guinea pig of Group 2, Brucella was recovered from the internal organs.

Thirty-one days after infection, within 24 hours after penatin therapy was discontinued, one-half of the surviving animals in each group were killed, while the remaining guinea pigs were killed 1 week later. In each instance the spleen, liver, kidney, and inguinal lymph gland were cultured, and all but 2 animals yielded *Br. abortus* on cultures of one or more of these tissues. The 2 guinea pigs which did not show Brucella on cultures had ruptured stomachs at the time of autopsy which caused contamination of the internal organs, and consequently contamination of the culture plates, making isolation of Brucella impossible. The following table indicates the number of animals in each group autopsed after the penatin treatment was completed, and the results of cultures of the tissues.

TABLE 3.—CULTURE FINDINGS IN AUTOPSIED ANIMALS

	No. animals in group	Autopsied after penatin treatment was discontinued		Culture findings
		24 hours	1 week	
Group 3	9	5	4	8 positive 1 contaminated
Group 4	10	5	5	9 positive 1 contaminated
Group 5	8	4	4	8 positive
Group 6	8	4	4	8 positive
Infected untreated guinea pigs	21	10	11	21 positive

In addition, 2 guinea pigs from Group 2 which had survived the first 2 days of penatin injections and had recovered from the toxic effects were killed at the same time as the second half of each of the above groups. *Br. abortus* was isolated from both animals.

Summary of Part II. Subcutaneous injections of 80,000 units and 40,000 units of penatin twice daily proved highly toxic for guinea pigs, and most of the animals thus treated died after the third or fourth administration of the material. A lower dosage, *i. e.*, 10,000 units of penatin injected twice daily produced local toxic effects, but did not prove fatal to guinea pigs treated for 30 days; whereas animals treated for the same length of time with doses of 1000 units and 200 units did not show any ill effects from the treatment.

The largest sublethal doses of penatin used, *i. e.*, 10,000 units twice daily, as well as the smaller doses, *i. e.*, 1000 units and 200 units twice daily, injected subcutaneously for 30 days, beginning 24 hours after infection, did not have any therapeutic effect on guinea pigs infected with *Br. abortus*. All the treated guinea pigs, with the exception of 2 whose cultures were contaminated, and all the controls yielded *Br. abortus* on cultures.

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Prolonged injections of 10,000 units of penatin twice daily impaired the growth of the guinea pigs, and their increase in body weight was less than one-half that of the animals in the other groups. The animals injected with this dosage showed considerable anorexia throughout the period of treatment.

These results, as well as those published in Part I of this article, show that penatin is toxic, and when administered in sublethal doses is not effective in treating Brucella infection in guinea pigs.

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LEPTOSPIROSIS

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Weil's disease is a specific febrile spirochetal infection caused by *Leptospira icterohæmorrhagiæ*. In various parts of the world this organism is common in rats, which constitute a natural reservoir and a source of human infection. The disease is characterized by a sudden onset with rather high fever, headache, and vomiting. Jaundice is common and the urine almost always contains albumin and bile. Hemorrhages, especially epistaxis, are common, and the liver and sometimes the spleen show enlargement. Polynucleosis is present.

The disease is known by several names as leptospiral jaundice, spirochetal jaundice, epidemic jaundice, spirochætosis icterohæmorrhagica, typhus bilieux and Weil's disease.

This form of jaundice was first recognized as a distinct disease by Weil in 1886, who described it as an acute infectious disease characterized by jaundice, swelling of the spleen and nephritis. Inada and his Japanese colleagues[43] discovered the causative spirochete in 1915, and in 1917 injected guinea pigs with the organism. Noguchi,[76] who thought that the organism was the cause of yellow fever, named it *Leptospira icterohæmorrhagiæ*. Laboratory methods to diagnose this disease were introduced by Wadsworth[104] in 1922.

Many of the synonyms used for Weil's disease should not be used, because they give the reader a wrong impression concerning the disease. For instance, spirochetal jaundice is not an adequate term, since jaundice is present in approximately only two-thirds of the cases. Epidemic jaundice should be limited to acute catarrhal jaundice caused by a virus, which is really more epidemic in nature than Weil's disease. Leptospiral jaundice or leptospiral infections are general terms and include other types of leptospiral infections. It is true that these two latter terms do include Weil's disease, but they are not specific enough. There are other strains of Leptospira which produce disease in man. Technically speaking, infections caused by *Leptospira canicola* should not be called Weil's disease, since he described cases due to infections caused by *L. icterohæmorrhagiæ*. However, some authors consider *L. canicola* infections as cases of Weil's disease, but most workers consider the two infections separately and merely associate them in their writings.

In recent years a number of serologic races of leptospira have been

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reported. Schüffner[85] distinguishes 3 human strains in Europe: (1) the cosmopolitan *L. icterohæmorrhagiæ* in rat and dog and the cause of classical Weil's disease; (2) *L. canicola*, causing specific canine disease (occasionally transmitted to man); and (3) *L. grippotyphosa*, the infecting agent in the swamp fever of Eastern Europe. He believes that the clinical (non-icteric) character, the serologic, and the epidemiologic picture (appearing in well-defined epidemics) are features which separate swamp fever from the other leptospiroses. Other important leptospiral diseases are those due to *L. hebdomadis*, *L. autumnalis*, and *L. pyogenes*. *L. hebdomadis* is the cause of 7-day fever, a disease which occurs in parts of Japan and resembles a mild Weil's disease. *L. autumnalis* has been found in cases of a disease known as "Autumn Fever" or "Hasmi." This latter disease is also found in Japan. Vervoort[95] (quoted by Strong), in 1932, isolated the strain *L. pyogenes* from an outbreak of pseudodengue in Medan, Java. This disease was endemic in plantation areas, and was associated with a mild rash and jaundice in most of the cases.

The spirochete causing Weil's disease, *L. icterohæmorrhagiæ*, is the type species of a genus described by Noguchi as having minute elementary spirals running throughout the body and failing to show either flagella or undulating membrane. The caudal portion of the spirochete is remarkably flexible, and when in motion the whole body seems drawn into a straight line except for the hook formation of one or both terminal portions. Propulsion seems to occur by the rotary motion of the hook, and progresses in the direction of the straight end. If both ends become curved, progression ceases. It is said to be insoluble in 10% saponin, thus differing from the other blood spirochetes. It is actively motile and often bends itself in the form of a hook, giving the appearance of the letter C when the hooks are on the same side, or the letter S. The organism varies considerably in size, averaging 6 to 14 microns. The constituent spirals are closely placed together, giving the appearance of small dots. The organism has been cultivated on Noguchi's leptospira media. It prefers a partial oxygen tension and usually grows in the narrow zone just below the surface. The optimum temperature for growth is from 25° to 30° C. Because of the universal use of Schüffner's culture media for this organism, it is important to mention its ingredients. It is composed of tap water 1500 cc., Witte's peptone 0.15 gm., Ringer's solution 300 cc., and Sovenson's solution pH 7.2. The final reaction of this peptone medium should be between pH 6.8 and pH 7.2. Three cubic centimeters of this medium are placed in a small tube and sterilized, and for use 3 cc. of rabbit's serum are added. The tubes are then heated to 56° C. for 30 minutes and incubated at 37° C. overnight. The organism can also be grown on other forms of blood agar. The leptospiræ are able to pass through the ordinary types of Berkefeld filters. Inada has obtained filtrates in which no spirochetal forms were demonstrable, but which were infective for guinea pigs. He believes, therefore, that there may be a viable, granular form.

American and World Incidence. Weil's disease is found in practically every country in the world, excluding countries where the temperature is always low. The disease is far more common in the tropic and temperate regions of the globe. It has been common in Japan and Egypt, and is also endemic along the North African coast and the shores of the Mediterranean, in West Africa and the Congo. Cases have been observed clinically in the Sudan. However, some workers were unable to find the disease prevalent in Egypt, Arabia or Persia.

In 1939 there appeared a review from the Netherlands by Walch-

Sorgdrager[105] in which 374 cases were extensively studied. The number reported in England, France and Germany runs well over 1000. It has been found to be relatively common in Denmark, Austria, and parts of South America. Walch-Sorgdrager lists 46 countries in which the disease has been described. Snapper and co-workers[89] report for the first time 2 human and 5 canine cases of leptospirosis in China. Lesh[59] gives a report of a case from Nigeria. He also states that the disease is present in the Canary Isles. This is the first time the disease was definitely proved to exist there. Gardner,[30] in 1940, gives a report of a classical case of Weil's disease in Melbourne, Australia. Lahiri[52] mentions that the disease does exist in Bombay City and cites several instances. Sixty controlled cases were discussed by D'Silva.[21] These cases of Weil's disease were present in and about the Andaman Islands. Some other places in the Far East, where recent reports of leptospiral jaundice with bacteriologic diagnosis have been made, include the Dutch East Indies, Borneo and the Celebes, Cochin China, Indo-China, and the Malay States.

In recent years, sporadic cases have been reported in London and Scotland, and outbreaks of the disease have been described in coal miners in Scotland, in Wales, and Northeast England; in sewer workers of London, Liverpool and Glasgow; in fish workers of Aberdeen, and in tripe workers in Glasgow.

In the United States the disease has apparently been comparatively rare. In 1935, Jeghers[45] reviewed the American literature, and found only 11 reported cases. In 1937, Packchanian found 32 proved cases.[77] Eighteen of these were from other observers, and 14 were his own. According to Ashe[3] in 1941, there have been reported about 35 other cases since 1937, making a total of 67 cases. In 1942, Harris[37] gives a total of 87 cases reported in the United States. In 1944, Senekjie[87] reported 30 cases of this disease from New Orleans, and these 30 cases plus the many case reports from all over the country in the past 2 years gives a total of over 100 cases reported in this country at the present time. Senekjie determined that the ratio in his series of cases was 1 case of leptospirosis to every 8445 general admissions and 1 case to every 1343 medicine admissions at Charity Hospital in New Orleans. Blake[6] reports a fatal case of leptospirosis in Connecticut in 1940. It was the first case ever to be reported from this State. In 1943, Bruno and co-workers[10] reported on the salient features of 15 cases of Weil's disease that were observed at Charity Hospital. Two of the cases had Canicola fever. Their work covered a span of $2\frac{1}{2}$ years. Reid and Holt[82] report a total of 13 cases in Virginia up to October, 1941. Bloom and Walker[7] also reported, in 1941, 7 cases of Weil's disease in Virginia. These 7 cases were observed in this State during the past 5-year period. Jentgen[46] reports a case from Ohio in 1941. Lester[60] gives a clinical and epidemiologic report of 14 cases of Weil's disease that occurred in a single mine in north central Alabama between March, 1938 and September, 1940. The work was published in 1942. Tiffany and Martorana,[97] in 1942, did a serologic survey for Weil's disease on 1351 individuals. They concluded that this disease, although endemic and sporadic in New York City, seems to have been usually unrecognized. Ward,[108] in 1942, reports cases in poultry dressers from Baltimore.

A question which always arises when Weil's disease is discussed is—Why is the disease more common in Europe when essentially the same conditions exist here as in Europe? The reasons for this discrepancy are probably numerous. In general, our laws do not provide for a more satis-

factory elimination of rats than is carried out in France, England, and Germany, though it must be admitted that our sewage disposal systems make it less likely that the excreta of sewer rats come into contact with those employed to maintain the sewer systems. There is no reason to suppose that North Americans are immune. Meyer,[67] in San Francisco, has found that when Weil's disease is carefully searched for, it is not difficult to find. There are 5 main reasons why the diagnosis is missed so often: (1) American Medicine textbooks have described the disease poorly, emphasizing chills and splenomegaly, which are rarely present. (2) Most city and state health laboratories are not equipped to make the diagnosis. (3) Most doctors have considered the disease too rare to include in their differential diagnosis. (4) Few physicians are aware that only 60 to 66% of the cases have jaundice. Finally, (5) In those few laboratories in which clinicians have attempted to prove the diagnosis, they have frequently failed, because they have not been familiar with the precautions which must be taken in order to establish the diagnosis in each of the 4 distinct stages of the disease.

Epidemiology and Endemiology. *L. icterohæmorrhagiæ* is found in the excreta of more than 10% of adult common gray rats.[45] It has been found not infrequently in dogs,[6,33,80,85] and is known to be present in field mice,[105] cats,[1] pigs,[19] foxes,[19,22] mongooses,[1] minks and bats,[80] poultry,[48] in the bandicoot[95] and in horses. All authors agree, however, that the vast majority of known cases of Weil's disease come from direct contact with the excreta of rats.

Human infection may result from the ingestion of food or water contaminated with the urine of infected rats. The leptospiras occur in the urine, kidneys and feces of wild rodents, especially *Mus norwegicus*, *M. alexandrinus*, *M. rattus*, the mouse, *M. musculus*, and the vole of Japan. In Europe, Schüffner believes the sewer rat, *M. norwegicus*, is especially concerned.[85] He found all the local epidemics he studied were usually accompanied by heavy murine infections, up to 56%. He considers that human infections are the result of contamination of the water by the urine of the infected rats. The percentage of infection among older rats was found to be always greater than in the young rats. In the younger animals the infection might be 3%, while in the adults up to 45%. This agrees with the work of Larson[56] in this country, who trapped wild rats in and about Washington, D. C., and found a greater incidence of infection among specimens over 20 cm. in length than among those of smaller size. He found the most reliable method for the detection of the organism among rats to be serologic examinations of their sera, and studies of Levaditi-stained sections of their kidneys. It has been suggested that the disease was primarily epizoötic in wild rats, but that these rodents have become tolerant and that some of them may harbor the parasite throughout life. It is regarded probable that the infection may be passed from one rat to another by way of food polluted with urine, and by sexual intercourse. Human infection may also occur from the bites of rats.[48] A case is reported by Varadi[103] where a young soldier in the British Army contracted the disease by merely handling a rat trap. This was his only contact. Lewis[61] gives a report on the incidence of *L. icterohæmorrhagiæ* in trapped rats in Philadelphia in 1942. He demonstrated the organism in 11 out of 100 wild rats, *M. norwegicus*. The organisms were capable of giving symptoms of a leptospiral infection in guinea pigs. Inoculation of guinea pigs from kidney emulsion technique was 90% efficient, as compared with a low per cent of "positive takes" obtained by other means.

In Bombay City in 1941, Lahiri[51] demonstrated leptospiras in the kidneys of 11 rats out of 125 rats trapped in the city. He used direct dark-ground illumination to demonstrate the organisms. Two other animals showed evidence of infection serologically. The rats found to be infected were all of the species *Rattus norwegicus* except 1 which was of the species *R. rattus*.

Rats carry the organisms in the tubules of their kidneys and excrete them with the urine. Soil, food, and water contaminated with rat urine can become a potent source of infection. The causative organism will live for a period longer than 3 weeks[16] in stagnant water which is neutral or slightly alkaline. Van Theil[102] in 1937 found that during the summer season of warmer weather *L. icterohæmorrhagiæ* survived for at least 22 days after infection of the water, and that its virulence remained intact at least as long as that. Lester,[60] in studying 14 cases in Alabama mine workers, noticed that the hydrogen-ion concentration of the pools of water found in the mines was between pH 6.9 to 7.9. By experiments, he showed that leptospira could live a long while in water with this pH. Leptospira do not live in media that are distinctly acid, and are not found in water of pH 6.7 or less.

In some localities it is thought that dogs may constitute a reservoir of human infection. Schüffner[85] and Meyer[67] were able to isolate *L. canicola* from persons suffering from an infection resembling Weil's disease. Although doubt is expressed regarding the possibility of acquiring *L. icterohæmorrhagiæ* infection from a dog source, this question needs further elucidation. Meyer also points out that *L. canicola* was not found in the rat population, so that the host relationship of the 2 spirochetes in California is apparently the same as in Holland, rats being the source of typical Weil's disease due to *L. icterohæmorrhagiæ* and dogs the reservoir for *L. canicola*. In the rare cases of human disease in which the infection has been acquired from contact with the dog, *L. canicola* has been the infection organism. Jaundice has not been noted in Europe in this form of human disease, though Meyer found jaundice in a percentage of his dogs and in human case. The susceptibility of dogs to infection with *L. icterohæmorrhagiæ* through contact with rats and the possibility that the dog may on occasion act as an intermediate vector between rat and man have received considerable attention by other workers.[6,67,68,85] Using the macroscopic agglutination test, Greene[33] showed that one-fifth of the dogs he selected at random in southern California had positive higher incidence of infection. The rate in the combined group of 368 dogs was 29%. No immune bodies against this strain was found in 100 serologic examinations in cats, or in 426 specimens from humans. Raven,[80] who reported on canine leptospirosis in Pennsylvania in 1941, also gives a report on the incidence of canine leptospirosis from 1930 to 1940 in the Netherlands, Belgium, Germany, Italy, and the United States. His figures for the United States are as follows:

Place	No. examined	% positive
New York	111	11.7
Santa Rosa	28	14.3
San Francisco	47	34.0
Pennsylvania (rural) (old dogs)	105	38.1
Philadelphia (urban) (young dogs)	50	28.0

Raven concludes from this study that since dogs excrete leptospira in their urine and there is evidence that from 11 to 38% of dogs in this country may be temporary or permanent carriers and shedders of leptospira, canine leptospirosis may become a public health problem.

The leptospira may gain entrance to man through the skin and mucous membranes, the conjunctiva, mouth and intestines. In outbreaks of the disease it has sometimes been possible to distinguish among the population certain groups of people more disposed to infection than others, and the disease has been discussed as an occupational hazard. Thus, it often occurs in people whose occupation leads them near water: barge men, wharf men, fish workers, slaughter house employees, poultry dressers, miners, garbage workers, abattoir workers, soldiers in trenches, rice field workers, in fact those who carry on their work in localities infected with rats. It is even stated that among swimmers the greatest risk is to those who swim the crawl stroke, since the possibility of oral infection is greatest in this particular method of swimming. Schüffner stresses that dissemination of the etiologic agent through water should be seriously considered. It is possibly conceded, however, that contamination of the unbroken skin with water containing the pathogenic strains of leptospira probably will not result in infection. The infection of water appears to be in no way proportional with the degree of visible contamination. Jorge (1931) reported an epidemic in Lisbon in which a leptospira was isolated from a public fountain. This indicates that the mouth and mucous membranes should be considered as important portals of entry for *L. icterohæmorrhagiæ*.

In the Netherlands,[105] it has been shown that 91% of the cases come from contact with water, and only 9% from those whose occupations necessitate the frequent handling of rats. However, in the United States, most of the cases reported have been in persons whose occupations demanded working in wet places where rats were common.[38,105] Stimson[93] and Lester[60] report the disease in miners who work in wet mines. Cushing[13] reports the disease in sewer workers. Havens[39] in 1941 reported 7 cases of Weil's disease apparently contracted by bathing in a stream polluted by infected rats. The disease expressed itself in varying grades of severity in these cases. Five were affected mildly, 2 severely, and 1 died. The diagnosis was proven by cultural studies and serologic evidence. Davis[17] in 1942 also reported a case where a man 25 years of age contracted nonicteric leptospirosis while bathing in water polluted by rats. Martmer[63] reports a case in a child where infection occurred *via* an infected dog. Meyer reports a similar case.

Of these workers who have studied the disease in Europe, Davidson,[16] and Hindle[41] indicate that one may expect to find the disease in all rat-infested places when water is permitted to remain for a period of time. In Rotterdam, Walch-Sorgdrager mentions 71 cases that have been reported from accidental falling into dirty canals, and also from swimming in local swimming pools where the daily exchange of water is not sufficient to keep the pool clean. Smith[88] writes that in Aberdeen it is so common among fish workers that it is known as the "fish worker's disease." Morrissey,[71] reporting from Australia in 1934, tells of a very high incidence of the disease among sugar-cane cutters. Tohyama[98] states that the incidence of the disease among rice field workers has been lowered in Japan since the use of acid fertilizer in the fields. As mentioned before, the leptospira do not tolerate a high hydrogen-ion concentration. The work of Hindle[41] and Alston[2] brings out the fact that fish workers and sewer workers are commonly infected in London and Paris. In England, Weil's disease is now considered an occupational disease in certain industries in which wet floors are unavoidable, and industrial compensation has been paid in a fatal case. In this regard, Stiles and Sawyer[92] in 1942

said that leptospiral infections may be considered as an occupational hazard, providing the occupation exposes the patient to rats or dogs, or to moist materials contaminated by the urine of these animals, and provided that the illness follow such exposure by the recognized incubation period of from 2 to 19 days. He states also that compensation for this industrial infection is therefore justified. Weil's disease has now been recognized as a compensable occupational disease in fish workers in New York.[27]

Weil's disease does not show any definite seasonal variation. Sporadic cases may occur throughout the year. It has been noted, however, that an increased incidence may be expected during the late spring and early fall. This is probably due to increased rainfall and consequent establishment of more favorable environment for the leptospira.

There are no reports in the literature of man to man infections. Man to man infections must be rare in spite of the fact that virulent organisms may be excreted in the urine for weeks. However, in spite of the rarity of occurrence, many authors mention that this still is a contagious disease and that physicians should take no unnecessary chances, but to take the usual precautions and treat the patient as if the disease were very contagious.

Of the reported cases in this country, more than 90% were males. This striking male preponderance is also common in Europe and in Japan. Out of Senekjie's 30 cases,[87] only 1 was a female. Seven of the 30 were colored, and the only female was a Negress. The age incidence of these cases was from 14 to 68 years. Most of these patients were admitted to the hospital from the 2nd to the 9th day after the onset of the disease, the average being from the 4th to the 6th day.

Walch-Sorgdrager[105] reported 363 cases from the Institute for Tropical Hygiene in Amsterdam, 323 were males and 40 were females. Smith and Davidson[88] have definitely shown that this is not a sex-linked susceptibility, but purely an occupational difference. In 210 fish workers tested, there were many more women with the disease than men, and in that group the proportion of women to men in the industry was 10 to 3. The ratio of infected workers was 19½ to 3.

In children, this disease is rare. Hindle and Brown describe[41] a small epidemic in children in England. In this country Martmer[63] reports the only case in a child. Walch-Sorgdrager reports the following age incidence in 370 collected cases:

Age	
1–10	11 cases
10–40	210 cases
40–60	49 cases
60 and over	15 cases
Age unknown	85 cases
Total	370 cases

Learn[58] states that the older the patient, the more severe the symptoms. There is definitely a higher mortality in the older age groups.

Clinical Features of the Disease. The clinical course of the disease may be divided into 3 or 4 stages. Different authors vary. There is no sharp line of demarcation between the several stages. However, these stages are important for diagnosis, and a thorough knowledge of the features of each stage is essential if one wishes to apply correctly the various diagnostic procedures.

The incubation period varies slightly according to different authors.

Senekjie[87] gives the incubation period as being between 1 and 2 weeks. The best evidence in determining the incubation period of the disease is found in accidentally infected cases among laboratory workers. Schüffner[85] found a range of from 4 to 19 days, with a mean incubation period of 9.5 days in all cases whether icteric or not. Inada[44] reports 5 to 7 days. Strong reports an incubation period of from 6 to 12 days (rarely up to 19 days). Ellenberg[24] gives an incubation period of 10 days, and Learn,[58] 1 or 2 weeks. Most all workers do agree that the length of the incubation period does not appear to be of prognostic significance.

Weil's disease is characterized by a high fever, chills, myalgia, arthralgia, prostration, jaundice, hepatomegaly, a hemorrhagic tendency, conjunctival injection, disturbance of heart function, and varying degrees of renal failure. The disease is essentially a hepato-renal syndrome. Some of the older writers consider splenomegaly to be an important finding, but all recent articles stress that the spleen is enlarged in only about 10% of all cases. In the anicteric cases, the liver damage is small; there is always, however, a hepatitis no matter how mild the infection. In the majority of cases there is a moderately severe hepatitis. Inada[44] found jaundice present in Japanese cases in about 60%. Greene and Farrell[33] in 1940, in a review of the literature on the liver and biliary tract, concluded that the pathogenesis of the icterus in Weil's disease is as yet obscure. It is not due solely to large biliary tract obstruction, as severe jaundice may occur with acholic stools. McNee[65] describes the morbid anatomy as showing considerable hepatic cell degeneration, granulation of the liver cells with vacuolation, pyknosis, and karyolysis. Cells with 2 nuclei and mitotic figures have also been described. He states that the mechanism of jaundice may in part be due to the hepatitis itself. In 1917, Stokes, Ryle, and Tytler[94] demonstrated marked inflammation of the smallest biliary ducts, and concluded that the jaundice was due to obstruction in these passages. Dawson and Hume[18] also in 1917 showed that in some instances there was no pathologic evidence of biliary tract obstruction. Dawson and Hume advanced the duodenitis theory of partial obstruction at the ampulla of Vater as the cause of the jaundice, but this idea is no longer held even by these two authors. One German writer, studying the liver physiology in infected guinea pigs, believed that the jaundice was due to extensive blood destruction with retention of bilirubin resulting from functional impairment of the liver, the latter due to edema of that organ. This work was based in part on the indirect van den Bergh reaction, but many workers have shown the reaction to be direct in humans. Walch-Sorgdrager,[105] studying European cases, show that any of the known van den Bergh reactions may take place, and that they are not predictable from a clinical study of any given cases. In a recent article by Learn,[58] he states that the jaundice is essentially obstructive in nature, but is not complete in many of the cases, as determined by the fact that some of the patients have only a light lemon tint to the skin and scleræ. Experimental work tends to show that this obstruction is due to the viscosity of bile and the low pressure under which it is excreted, permitting it to be reabsorbed. When the bile loses its viscid character, the flow is reëstablished and the jaundice disappears. From the available material it can be seen that the mechanism of icterus in Weil's disease is not entirely established. It is probably due in large part to true hepatitis, but it may also be contributed to by hemolysis and by intrahepatic biliary tract obstruction.

The kidney lesion may be mild, moderate, or severe, and is one of the

outstanding features of the disease. The urine early shows albumin, and in severe cases frequently shows red cells, casts and white cells. Oliguria is a common phenomenon, and anuria is not infrequently a cause of death. Urea retention begins early in the disease, and may be severe, the blood urea nitrogen reaching levels of 150 mg. % or higher. When severe, it is frequently associated with acidosis, again of renal origin. Jeghers[45] feels that the tubular damage is usually much more apparent than is the glomerular damage, and concludes that the extent of the renal damage is often better indicated by the clinical and laboratory findings than by the histologic structure of the kidneys. It is generally conceded that the renal damage, chiefly tubular, is toxic in origin and due to the spirochetes rather than to bile; this point, however, is by no means proved.

The hemorrhagic tendency is quite variable, but is a characteristic part of the clinical picture. There are cases reported, however, where evidence of hemorrhage have been absent.[105] Small hemorrhages have been described in nearly every organ in the body, but are most commonly found in the striated muscle, kidney, adrenal, liver, stomach, spleen and lung. Stokes[94] describes hemorrhages in the meninges of the brain and cord; they are rare in the brain. A review of the literature shows that early in the disease nasal hemorrhage is most common. Jeghers,[45] Walch-Sorgdrager[105] and McNee[65] all agree that the hemorrhagic diathesis appears to be due to primary capillary damages, and not to any disorder of the blood and its clotting mechanism. Ashe[3] has demonstrated decreased red cell fragility and normal bleeding and clotting times, as well as normal platelet counts and prothrombin time. White and Prevost,[109] in 1941, suggest that a prothrombin deficiency along with capillary damage may be responsible for the hemorrhagic state. Clapper and Meyers[12] in 1943 mention that the plasma prothrombin, although appreciably decreased in amount in most circumstances, usually does not reach levels sufficiently low to account for the hemorrhagic manifestations.

The Dutch physicians have emphasized the occurrence and importance of the flushed conjunctivæ. According to many writers, the most constant and typical sign of a mild Weil's disease is infection of the eyes.

Unlike most acute infectious processes, the severe muscular aching associated with tenderness of the muscles, especially over the back and in the calves, has in Weil's disease a pathologic basis which is one of the primary distinguishing features of the disease. According to Jeghers,[45] the lesion is most frequently found in the calf. This process characteristically selects isolated fibers and only part of a fiber as demonstrated microscopically.

The incidence of meningitis in Weil's disease is unknown because lumbar puncture has not been done in most instances unless the patient had clinical evidence of meningeal involvement. Most authors feel that routine punctures are indicated and will show a high incidence of mild meningeal involvement. The symptoms and signs vary widely in severity, but differ not at all from those of other mild and severe meningitides. The spinal fluid is usually under increased pressure, and the Pandy reaction is weakly positive. The cell count may range from 10 to 3000, but usually does not go above 200 or 300. The neutrophils and lymphocytes are about equal in number. The sugar and chlorides are usually normal, and the Wassermann reaction negative. Early in the disease the organisms are said to be demonstrable in the spinal fluid.[105] Clapper and Meyers[12] in July, 1943 studied 13 cases with particular reference to meningeal symptoms and signs. In only 2 cases were there both clinical and laboratory

evidence of meningitis. In 7 there was an abnormal cellular reaction in the spinal fluid without clinical signs of meningeal irritation, and in 1 case meningismus was present without the spinal fluid showing pleocytosis. He states that the cell counts of the spinal fluid may reach 1000 or more per mm.^{3} with neutrophils predominating early and lymphocytes later. The dextrose content of the spinal fluid is not altered, but the fluid may be discolored yellow due in part to the bilirubin present. No cases of pure spirochetal meningitis have been reported in this country.

The clinical stages of the disease are three or four in number depending on the author. I will discuss the disease in terms of four clinical stages, although I must admit that there is no absolute line of demarcation.

Septicemic Stage. The symptoms in this stage lasts about 3 to 7 days. Approximately two-thirds of the patients have as their symptoms, chills and then fever, nausea, vomiting, arthralgia, myalgia, frontal headache, prostration, anorexia, diarrhea or constipation. Epigastric pain and discomfort, pain and tenderness of the muscles of the legs and back, and painful ocular movements are very common. As there is often an upper respiratory infection with cough and bloody sputum this may simulate atypical pneumonia. The fever is usually high, being about 102° to 104° F. The respiration is normal or rapid, the pulse is rapid, and there is a tendency to hypotension. Senekjie[87] mentions that conjunctival injection was present in 50% of his cases. In this state, there are no noticeable hepatic or urinary disturbances, even though the fever is continued high. Leptospiras may be demonstrated in the circulating blood by means of dark-field microscopic examination, but at this stage there are no demonstrable circulating antibodies.

Hepatic or Icteric Stage. The duration of this stage is 7 to 10 days.[87] Icterus usually appears on the 6th to 7th day after onset. Some writers give the 2nd and 3rd day, and others say icterus may not be manifested until as late as the 9th day after the onset. The development of jaundice is gradual. As mentioned before, it is present in about two-thirds of all cases. The liver is enlarged, tender, and painful, and is usually about 2 fingers palpable. In Senekjie's report, 10% (3 cases) of the patients did not have an enlarged liver, but jaundice was present. In his 2 anicteric cases, the liver was palpable, and hepatitis was present in both.

The spleen is enlarged in 10% of the cases, is very soft, and when enlarged it extends 2 to 4 cm. below the left costal margin. It may be compared to the spleen seen in typhoid fever patients.

During this stage, gastro-intestinal symptoms have a tendency to subside. Vomiting, arthralgia, myalgia and headache are not particularly distressing, but the patient is usually toxic, apathetic, prostrated, and has a continuous fever. There is moderate abdominal distention due to a varying degree of ileus and diminished peristalsis.

In Senekjie's[87] cases, hemorrhagic phenomena were noticed in 16 cases (53.6%). There is often seen conjunctival injection, hemorrhages into the eyes, petechial hemorrhages and ecchymotic spots in the skin and mucous membranes, epistaxis, melena, hematemesis, hemoptysis, and gingival bleeding. No definite rash is ever noticed.

With the appearance of jaundice the pulse rate decreases. Pruritus is, as a rule, conspicuously absent. Herpes labialis is, as a rule, not found. There is no general lymphadenopathy.

Respiratory symptoms are present in about half of the cases. These patients have a cough, expectorate a great deal (rarely blood-tinged), have pharyngitis, bronchitis, and a patchy consolidation of the lungs. Most of

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these cases are diagnosed as a viral pneumonia before the jaundice and characteristic urinary findings set in.

The cardiovascular system is usually affected during this tage. There is a tendency toward hypotension, and the blood pressure therefore is usually lower than normal. At times the heart actually becomes dilated, and hemic murmurs are not uncommon. Gallop rhythms, bradycardia, premature beats, auricular flutter and fibrillation, and pericardial friction rubs have all been described in Weil's disease. The electrocardiogram may show a prolinged QT and PR interval, defective AV conduction, functional or real incomplete AV block, low T waves, blocked auricular beats, sinus tachycardia, and a QRS complex which is low in voltage, is wide and slurred. It is a reversible type of heart disease, and in most cases the heart returns to normal during convalescence.

Central nervous system complaints include headache, delirium, apathy, hallucinations, disorientation, and restlessness. In the very severe cases the patient has a stiff neck with retraction of the head, a loss of consciousness and some of the other characteristic signs and symptoms of meningeal irritation.

Nephritic or Uremic Stage. Transition from the hepatic to the nephritic stage is not clear-cut. In fact, many authorities on the subject combine the hepatic and nephritic stages. During the septicemic stage there is a mild albuminuria, some diminution in urinary output, and an occasional red and white cell. During the hepatic stage, there is some degree of oliguria. In the urine there are found red and white blood cells and occasional casts. In this stage there is no retention of metabolites in the blood. At the onset of the uremic stage practically all patients have oliguria while a small percentage has anuria. In all fatal cases, anuria seems to be a constant finding. Albumin is present in large amounts in the urine, and there is glycosuria in about 10% of the cases. Red and white cells and granular casts are present in large numbers. There is a steady rise in blood pressure, a retention of nitrogen metabolites, and a definite decrease in kidney function as shown by the various kidney function tests.

Convalescent Stage. As the name implies, during this stage the patient is on his way to recovery. The jaundice begins to leave, and the uremic stage improves. More urine is secreted, the temperature returns to normal, and hemorrhages stop, but the patient stills feels rather weak. Ordinarily convalescence is in the 3rd week, but it may not occur until the 5th to 6th week in certain cases. The last sign to disappear is jaundice which might persist for weeks. Relapses occur in about 20 to 25% of all cases, and this happens usually from the 3rd to the 5th week after the beginning of the disease.

Laboratory Findings. 1. *Hematologic Findings.* There is usually a microcytic hypochromic anemia present, the cells averaging 1.8 to 3.5 millions in number. Ashe[3] states that the platelets are normal in number and that the prothrombin time is normal. Most workers, however, agree with Senekjie,[87] who states that there is a slight reduction in the number of platelets, and that the prothrombin time shows moderate to marked prolongation. The bleeding and coagulation times are normal. The red blood cells do not show increased fragility. In fact, some authors state that the red blood cells show decreased fragility. The sedimentation rate is increased. As a rule, all authors report an active leukocytosis with an increase in polys and a shift to the left. Senekjie reports an active leuko-

cytosis of 10,000 to 30,000 in 83.4% of his cases. Six of his cases had a normal white blood count.

2. *Blood Chemistry.* There is a high and rising icteric index as the bilirubin blood level reaches 300 units and 90 mg. % respectively. The van den Berg reaction has been reported both as direct and indirect. Senekjie reports the van den Bergh reaction as being direct. Most authors disregard the van den Bergh reaction in this condition since it is not constant, and is of little diagnostic significance.

The chlorides, sugar, and cholesterol levels are normal. The urea and uric acid levels rise and reach their peak during the nephritic stage. Blood urea nitrogen levels of 50 to 100 mg. % are common, and Ashe reports some cases with blood levels of 150 mg. %. The serum proteins are slightly decreased. Late during the course of the disease the creatinine blood level rises. Senekjie mentions that a 10 mg. % creatinine level is a bad prognostic sign, while a level of 12 to 14 mg. % usually means that the patient will have a fatal outcome. The carbon dioxide combining power is normal or decreased. The hippuric acid test for liver function is somewhat reduced, and the cephalin-flocculation test is usually positive.

3. *Urinary Findings.* In all cases there is some degree of oliguria. In fatal cases there is complete anuria. Albumin, red and white cells, hyaline and granular casts, bile pigment and excess urobilinogen is present. Glycosuria is present in only a few cases. Kidney function tests show an impairment of kidney function.

4. *Spinal Fluid Findings.* These were mentioned before when leptospiral meningitis was discussed.

Pathologic Findings. During the septicemic stage, the spirochetes invade the internal organs such as the liver, adrenals, kidneys, muscles, prostate, thymus, appendix, testicles and epididymis. However, the early immunologic response in man leads to destruction of leptospiras in all the organs except the kidney and heart muscle where they can be demonstrated histologically.

Liver. There may be little or extensive change in the liver. In mild infections, there is merely biliary stasis, accumulation of leukocytes and lymphocytes in the portal spaces, cellular hyperplasia, and accumulation of hemosiderin. On the other hand, in severe infections, the destruction is seen grossly, with hypertrophy, loss of lobular markings and microscopically, coagulative necrosis, biliary stasis, fatty degeneration, marked macrophagic reaction, cellular reaction, and cellular infiltration; the hepatic cells are markedly altered, the normal cell structure absent and the sinusoids congested. The connective tissue reaction is never remarkable.

Kidney. Grossly, there is frequent hypertrophy, icteric coloration, variable hemorrhages and, in protracted infections, fibrosis. Microscopically, the lesions may be multiple; the tubular portion is most affected with necrosis and many casts. The glomeruli are often swollen and filled with exudate and bile precipitate; the capsular endothelium is proliferated. There may be fatty degeneration, cellular infiltration and edema of the interstitium. The proliferation of the connective tissue and fibrosis in protracted cases may be very severe. Hemorrhage may be so marked as to simulate hemorrhagic nephritis.

Heart. Occasionally, there is cardiac hypertrophy, often ecchymoses of the epicardium and endocardium. Microscopically there is subendocardial hemorrhage and round cell infiltration of the myocardium. In cardiac collapse, there is also vacuolar and granular degeneration of contractile fibers.

Lungs. Grossly, there is petechiation of the lungs and pleura. The parenchyma is edematous; the tracheal mucosa is ecchymotic. Bronchopneumonia is a frequent complication. There may be intraälveolar and intrabronchial hemorrhages, areas of leukocytic infiltration, and active phagocytosis.

Intestines. The changes are difficult to gauge due to a postmortem autolysis. Microscopically, there are discrete hemorrhages, edema, cellular infiltration, and evidence of degeneration of the muscle coats. Sometimes, the pancreas is the seat of inflammation and hemorrhage.

Hematopoietic System. Grossly, the lymph glands are hypertrophied and hemorrhagic. The spleen is hypertrophied in some cases. Microscopically, the lymph glands show cellular proliferation. The spleen shows evidence of homogenization, thickening of the reticulum, cellular proliferation, a macrophagic reaction with collection of hemosiderin. There is only feeble erythroblastic activity and little proliferation of white cells. Hematophagia is marked in all the organs and is characteristic of leptospirosis. Hematophagia, together with the feeble erythroblastic activity, explains the anemia.

Nerve Tissue. Little change is noted in the nerve tissue excepting for occasional scattering of hemorrhage and cellular infiltration.

Eyes. There are hemorrhages in the conjunctiva, occasionally, the deep layers, the choroid, retina, optic nerve, and even the orbit. The blood-vessels are dilated. There is occasional cellular infiltration and keratitis.

Skin. In the skin there are sometimes cutaneous and subcutaneous hemorrhages and perivascular cellular infiltration.

Striated Muscles. There is evidence of degeneration of muscle fibers, cellular infiltration and hemorrhage, these changes are most marked in the calf muscle.

Suprarenals. Early in the disease there is hemorrhage throughout the gland; later there is infarction. The parenchyma is infiltrated with round cells and leukocytes.

Summarizing this section, it is evident that the most severe pathologic lesions are in the kidney. When the liver is markedly affected, the combination (together with the changes in the kidney parenchyma) may be termed the hepatorenal syndrome. This syndrome is characterized by abundant karyokinesis in the liver and kidney cells and especially by the extensive hematophagic reaction.

Diagnosis. The diagnosis of Weil's disease is made by a careful study of the clinical findings and by means of certain laboratory procedures. As in typhoid fever, the procedures necessary to establish the diagnosis of Weil's disease vary, depending upon the duration of symptoms.

A presumptive diagnosis can be readily made in a majority of cases presenting (1) the classical symptoms of sudden onset of chills, headache, fever, arthralgia, myalgia, injection of the conjunctivæ, the hemorrhagic phenomena, and leukocytosis. (2) Hepatomegaly, and jaundice on the 5th to 7th day of the illness. However, anicteric cases must be considered. (3) Albuminuria, casts, and evidences of kidney failure with retention of metabolites in the blood. (4) A definite history of exposure. However, the final proof that the patient has Weil's disease must come from finding the causative organism in one way or another. It is because of the protean nature of the disease that all clinical diagnoses must be proved by the laboratory methods of diagnosis.

Accurate diagnosis is made in the laboratory and depends upon: (1) detecting leptospiras in fresh blood, (2) by culture from the blood, (3) by

inoculation of the blood into a suitable laboratory animal, (4) detection of the organism in the urine and the inoculation of laboratory animals with it, (5) serologic examination, (6) Fontana and Levaditi stains of tissues, and (7) muscle biopsy.

Before a discussion of these various laboratory procedures is made, it might be well to mention a statement from an article by Reid and Holt.[82] They say that emphasis should be placed on the fact that no single laboratory examination has proven entirely satisfactory for the diagnosis of Weil's disease because of some fallacies in each test.

1. *Dark-field Examination.* During the septicemic and hepatic stages, a dark-field examination of the patient's blood is the best method of diagnosis. Strong[95] emphasizes that in every suspected case, a search should be made with the dark-field illumination for the leptospira. He also mentions that thick films may also be stained by Giemsa's solution for examination. The technique consists of examining blood under dark-field illumination with either the usual high dry lens or the oil-immersion lens of the average microscope. *L. icterohæmorrhagiæ* appears as actively motile spirochetes. The characteristics of the organism have been described in the early part of this paper. The only difficulty one encounters in identifying the organism is the presence of myriads of minute particles of fibrin and other partially precipitated protein normally seen in blood which are in constant Brownian motion. Schultz[86] observed parts of degenerated red cells and pieces of fibrin which resembled *L. icterohæmorrhagiæ;* he called these pseudospirochetes and emphasized the importance of having an experienced pathologist confirm all suspicious findings. Fortunately for diagnostic purposes, Ashe[3] says that when *L. icterohæmorrhagiæ* is present in the blood, it is usually present in large numbers. Also, that incubation at 27° C. (in the vest pocket) will frequently increase the number of organisms in the specimen and facilitate demonstration. Strong,[95] on the other hand, says that the organisms are rarely numerous and are only present during the first days of illness, so that they are frequently not detected. Better results have been obtained by centrifuging fresh citrated blood, but Schüffner[85] has emphasized the difficulty of precipitating the spirochetes even at high speeds. Some workers advocate triple centrifugation. Of Senekjie's[87] cases, 23% were diagnosed by dark-field examination.

In the 2nd week of the disease the spirochete may be occasionally found on direct dark-field examination of the cerebrospinal fluid. Because not infrequently there are spirochetes of many varieties in normal urine, direct dark-field examination of urine is not satisfactory.

2. *Animal Inoculation.* For therapeutic reasons, it is most desirable to demonstrate the organism directly in the blood stream in the 1st week of the disease, because it is during this period that specific therapy is most valuable. In the early part of the disease, blood from the patient is used; in the later days of the disease, it is better to use the urine.

For this procedure, it is necessary to choose the proper laboratory animal. Now any animal will do. The most common animal used is the guinea pig, one weighing 175 gm. or less. Unfortunately, not all guinea pigs will die when inoculated. They must be young. Das Gupta[15] showed that young guinea pigs born of mothers actively immune to leptospiral infection exhibit marked resistance against homologous infection. This resistance persists until the 62nd day after birth, but not up to the 188th day. He suggests that the female guinea pigs which have acquired immunity by some means or other should not be used for breeding pur-

poses, as the young borne of these animals are unsuitable for diagnostic inoculations. Morton[72] prefers to use white mice or Syrian hamsters. Young white mice are very susceptible to *L. icterohæmorrhagiæ*. The death rate in inoculated animals is appromately 100% in 3 week old mice, but this high mortality rate falls off rapidly if older mice are used. Although Morton limited his work to 1 strain each of the 2 species of leptospira, it appears that Syrian hamsters may be useful as laboratory animals in work with *L. canicola* and *L. icterohæmorrhagiæ*. Reid and Holt[82] (after Packchanian) suggest the use of certain species of deer mice as suitable susceptible small laboratory animals for experimental studies of icterohemorrhagic spirochetosis, and for the diagnosis of Weil's disease.

In some instances, leptospiras have been detected in the blood as late as the 8th and 10th day. When not found in the blood, 3 to 5 cc. of it or of centrifuged plasma should be inoculated into the peritoneal cavity of the guinea pig. The animal usually dies in 10 to 12 days, with characteristic pathologic lesions. Schüffner[85] states that the leptospiras can frequently be detected in drops of fluid from the peritoneal cavity of the animal after several days, usually being present by the 3rd. The organisms can be demonstrated in the liver, the lung, and the kidney of the animals, either by section and staining with the Levaditi or Giemsa stains, or directly by dark-field examination of an emulsion of these organs. Rathbun and Waghelstein[79] realize that different strains of the organism vary in virulence. They recommend that if the inoculated guinea pig does not die by the 12th day, it should be killed, and that further guinea pigs should be inoculated with the blood, liver, and kidney of the initially inoculated animals. Three such passages should be carried out before a negative report is made. Exact identification of the strain of spirochete must, of course, be done serologically.

After the 1st week of the disease, leptospiras should be searched for in the urine. They are usually most prevalent from the 10th to the 20th day of the disease. Centrifuged sediment of fresh urine should be examined directly at first, and then guinea pigs should be inoculated with it. This latter method has proven unsatisfactory in many hands, and is probably one of the very important reasons for failure to establish the diagnosis in this country. In order to assure good results, Ashe[3] gives the following precautions: (1) The urine must have stood not more than an hour before the inoculation is made. (2) Strongly acid or strongly alkaline urine quickly destroys *L. icterohæmorrhagiæ*, and the patient must be given some agent to make his urine approximately neutral when voided. (3) The guinea pig must be young (175 gm. or less).

3. *Agglutination Reactions.* In the 3rd and subsequent weeks of the disease, *L. icterohæmorrhagiæ* produces in the host very specific agglutinins which can be measured.[67,85] These are among the most specific antibody reactions known. Schüffner[85] believes agglutination tests are best carried out with leptospira cultures preserved in 5% formalin, as they do not lyse so readily as the living organisms, and he has found that the killed leptospiras agglutinate up to the highest dilutions compatible with the strength of the serum. If living leptospiras are used, agglutination appears only in the lower dilutions, as in the higher ones lysis sets in, rendering agglutination impossible. However, sometimes the formalized organisms are often rendered unsatisfactory for the test after some weeks, since the leptospiras usually become matted together into feltlike clots.

In the average case, according to Ashe,[3] after 3 or 4 weeks the blood serum of the patient will agglutinate avirulent culture of *L. icterohæmor-*

rhagiæ in dilutions of 1:10,000 to 1:300,000, and will not agglutinate any other known strains in a titer above 1:250. This agglutination reaction is useless before the 9th or 10th day of the disease, because no specific antibodies are found. When found in high titer after the 14th day, it is diagnostic. Senekjie warns of the possibility of one being misled by an amnestic reaction in a patient, but serial agglutination tests showing a rapidly increasing titer serves as an accurate diagnostic test. Tiffany,[97] in discussing the agglutination test for Weil's disease, says that a titer of 1:1000 indicates a present or recent infection, but when found by an experienced technician, any titer, however low, merits investigation. Packchanian and Tom,[78] in reporting their cases, found the average level of agglutination titer during the active phase of the disease to average 1:23,000. Most observers now agree that the agglutination in dilutions of 1:300 or above is diagnostic. Senekjie[87] reports that 24 of his cases, or 80%, were diagnosed by means of the agglutination reaction. He found the titer of antibodies to be rising during the hepatic stage, reaching the diagnostic level at the nephritic stage. The peak was reached during convalescence. A summary of the agglutination titers found by Senekjie in these cases is as follows:

No. of cases	Agglutination titers
10	1:300–1:1000
3	1–3000
3	1–10,000
1	1–30,000
2	1–100,000
5	1–1,000,000

All workers in the subject agree that strong false positives are non-existent. A negative reaction after the 30th day of illness rules out Weil's disease.

There are three main types of agglutination tests: (1) the microscopic, (2) the macroscopic, and (3) the agglutination absorption test. Brown and Broom[8] think that the macroscopic test is not nearly as sensitive as the microscopic, and that in certain serums of low titer, such as those shortly after the 6th day of the disease, the reaction may not appear if the macroscopic test only is employed. Starbuck and Ward,[91] in February, 1942, made a comparative study of the results obtained with a newly developed macroscopic agglutination test and the standard microscopic agglutination test against *L. icterohæmorrhagiæ* on 356 human serums and 10 immune rabbit serums. They concluded that the macroscopic agglutination test against *L. icterohæmorrhagiæ* is specific and sufficiently sensitive to be of value in the diagnosis of acute cases of leptospirosis. They mention, however, that in an epidemiologic survey, that the standard microscopic test would probably be preferable since former cases of leptospirosis or inapparent infections might not be detected by the macroscopic method. Brown[9] describes a rocking-slide test, a type of macroscopic agglutination test. The test essentially consists in rocking to and fro on a slide for 10 minutes small quantities of varying dilutions of the patients' serum in the presence of a heavy suspension of *L. icterohæmorrhagiæ;* this saline suspension is formolized to a concentration of 0.2%. The dilutions of the serum are made in the depressions of a painter's palette. They are then mixed with an equal volume of antigen and placed on a slide just over the depressions in the palette. This is made to rock for 10 minutes, and the result is read by means of a hand lens against a dark background. The results of this method and the plain macroscopic have been con-

sistently identical, but in every instance Schüffner's microscopic technique has given a titer three times higher than that obtained by either of the other methods. However, the rocking-slide method, given a suitable antigen, will produce a result within 15 minutes of the recipt of the serum, and that it is reliable enough to justify the administration of serum.

Schüffner[85] and others merely used the agglutination absorption test to differentiate various strains of leptospiras. Senekjie mentions Lederle's slide agglutination antigen for the quick diagnosis of the disease, but he says that it requires checking with the regular agglutination technique.

4. *Complement Fixation Test.* Ashe[3] mentions that complement fixation reactions have been described but are less simple of interpretation, and he recommends the agglutination test as diagnostic. Kramer[50] merely mentions that the complement fixation test is helpful, but does not evaluate it.

5. *Culture.* Some workers believe that the diagnosis is most easily made from cultivation, in the incubator, by direct inoculation of the blood into blood agar. Schüffner[85] also recommends culture as a desirable method of diagnosis. By using this method, he cultivated the organism from 51 cases, of which 18 were without jaundice.

6. *Muscle Biopsy.* This does not seem to be very practical, although Blake[6] recommends biopsy of the gastrocnemius muscle when the diagnosis is otherwise doubtful. Vacuolation, swelling, loss of striations and hyalinization of isolated or groups of adjacent muscle fibers and infiltration with histocytes, neutrophils, and plasma cells may be seen on microscopic examination.

7. *Levaditi, Fontana and Giemsa Stains.* When examining fluids, Fontana's stain is used. Levaditi's stain is used on tissues. These staining techniques are used chiefly in finding the organism in the tissues and fluids of a person who died of a disease suspected to be Weil's disease. More often, however, these stains are used to demonstrate the organism in the liver, lung, and the kidney of the experimental animal after inoculation in order to diagnose the disease.

Differential Diagnosis. Before discussing the diseases with which Weil's disease may be confused, it might be well to mention some of the more atypical forms of this disease as taken from various sources in the literature.

1. Malaria-like onset: fever lasting for 24 to 48 hours only; late albuminuria; hemorrhages during afebrile period.

2. Complete absence of pains: slight fever with prostration; albuminuria and jaundice. Very few cases of this type were reported.

3. The pneumonic or influenzal type with massive consolidation of one or both lungs. This type was reported rather frequently.

4. The "melena" type with fever and profuse hemorrhage.

5. The cerebral or meningeal type with early unconsciousness, and delirium.

6. The cardiac or nephritic type simulating acute congestive cardiac failure.

7. Intensely jaundiced type with "black vomit."

8. The "yellow fever" type with "black vomit."

9. The non-icteric type. The cases are generally mild. Many authors report about one-half of their cases being of this type.

10. Chronic meningeal and a chronic icteric form were encountered in about 10% of the reported cases.

There are quite a few diseases with which Weil's disease may be confused. I will discuss the differential diagnosis of the more common ones in detail.

Typhoid Fever. This is commonly diagnosed because in many cases the pulse may be relatively slow for the height of the fever. The absence of rose spots, the negative blood culture, the marked calf tenderness, and cells in the spinal fluid, will usually rule out typhoid. The incubation period of typhoid is usually about 2 weeks, and for Weil's disease it averages about 9 days.

Influenza. In mild cases in which no jaundice develops, many cases have gone, and will go, undiagnosed as anything but "la grippe." The chief aid seems to be that in influenza-like states the patient promptly feels better when the temperature drops; in Weil's disease the patient feels quite badly for several days after the temperature becomes normal. Vomiting is much worse and much more frequent than in influenza, and a careful study of the urine and blood may show minimal evidence of renal and hepatic disease which would otherwise be overlooked.

Septicemia. Weil's disease may be confused with septicemia in which jaundice is a symptom. Helpful in differential diagnosis are the presence of intense muscle pain and tenderness in the former and a positive blood culture in the latter. Sometimes the jaundiced patient who has septicemia does not have choline.

Acute Catarrhal Jaundice. Ordinarily patients with this disease have very few complaints. Lassitude, anorexia, slight abdominal distress, nausea, and occasional vomiting comprise the subjective manifestations. Often patients do not seek medical attention until their scleræ are observed to be yellow.

On the other hand, patients with leptospirosis usually become ill suddenly with a prostrating malady which closely resembles severe influenza, and seek medical attention before jaundice sets in. Icterus becomes deeper more rapidly in Weil's disease than in acute hepatitis. Severe muscular pain and tenderness, especially of the back and calf muscles, should lead to the suspicion of the existence of leptospirosis. If conjunctivitis and hemorrhagic and meningitic manifestations are present, the suspicion is strengthened. In acute catarrhal jaundice, the white count is relatively low and lymphadenopathy and a palpable spleen are the rule. The reverse is true in Weil's disease. Evidence of renal disease, meningeal involvement, and a hemorrhagic tendency are absent in catarrhal jaundice. In Weil's disease, the time of onset of the jaundice, 3 to 9 days after the beginning of severe symptoms, should lead one to search for the etiologic spirochete.

Yellow Fever. In severe cases in some parts of the world, the chief differential diagnostic problem is presented by yellow fever. In this country the problem should rarely arise. It is of interest that Noguchi[76] was led to believe that a spirochete was the cause of yellow fever, because he examined the blood of patients with Weil's disease in the erroneous belief that they had yellow fever. Geographic limitations on the occurrence of yellow fever will often rule out this disease. The course of the temperature is somewhat different in the two diseases. In yellow fever, after 2 or 3 days, there occurs a remission lasting from 3 to 48 hours, which is followed by a relapse during which a marked relative bradycardia is present (Faget's sign). Otherwise the symptoms are the same, as in the initial period of fever. The second febrile period lasts from 2 to 5 days.

Probably of greatest value in the differential diagnosis is the white blood cell count, for leukopenia is the rule in yellow fever. Albuminuria occurs in both diseases, but appears earlier in yellow fever and becomes more

severe each day. Inasmuch as death or recovery will have taken place before the results of mouse inoculation and protection tests are available, these procedures have little practical value.

Ashe[3] states that the characteristic intense facial flush and very red lips of yellow fever are not present in Weil's disease, and that the face of the patient shows anxiety instead of lethargy.

Relapsing Fever. The clinical differentiation between leptospirosis and relapsing fever also is very difficult. Fever, icterus, hemorrhage, muscle pain, and signs of meningitis are common in both diseases. The first febrile period in relapsing fever, and the first stage of Weil's disease, both last about 6 days; relapses occur in both diseases during the 3rd week. The spleen and liver are said to be enlarged in relapsing fever, whereas the former is rarely, and the latter is not usually, enlarged in leptospirosis. Leukocytosis is present in both diseases. The diagnosis of relapsing fever is based on finding large spirochetes in stained films of blood taken during relapses.

Acute Yellow Atrophy. This should be differentiated rather easily, because it usually begins as a mild disease with symptoms similar to those described as occurring in "acute infectious jaundice." The patient with acute yellow atrophy becomes worse at a time, after 2 or 3 weeks, when the patient with leptospirosis is recovering. A diminution in the extent of liver dullness and the presence of leucine and tyrosine crystals in the urine are of diagnostic aid.

Other possible confusing diseases of minor importance, as far as differential diagnosis is concerned, are syphilis of the liver, liver abscess, and blackwater fever.

Prophylaxis and Control. Wani[106] in 1933 prepared a vaccine by treating emulsions of injected liver or cultures with 0.5% phenol and refrigerating for 7 days. Twelve hundred and sixty-two miners were inoculated who showed a morbidity of 0.3%, while in the control non-vaccinated group the morbidity rate was 1.12%. The serums of such persons protected guinea pigs against lethal doses of leptospiras. Das Gupta[15] in 1942 also reported active immunity in man following injection of leptospira vaccine. In 1938, van Theil[102] used living avirulent strains of leptospira which were maintained in cultures for 8 years. He inoculated 5 persons with this strain. Four developed atypical attacks, but the fifth manifested icterus. He points out that this case proves that the injection of avirulent strains of leptospiras are not entirely without danger, and especially on account of the greater susceptibility of some individuals. According to Walch-Sorgdrager,[105] immunization with vaccines containing killed leptospiras has been used on a large scale in Japan by various workers with apparently some success. In addition, Alicata[1] has successfully immunized dogs against leptospirosis by the use of 0.2% formolized leptospira antigen. Senekjie mentions that it is not advisable to use living leptospiras, since we do not know the factors which enhance the virulence of the organism. He further states that, since the disease is only sporadic in the United States, there is no need for prophylactic inoculation here.

The prevention of the disease rests largely on the following measures:

1. Control of rats; these animals should be especially prevented from entering establishments where the floors are kept wet, such as basement shower-rooms.

2. Protection of feet by the use of boots or shoes whenever working in wet areas frequented by rats or dogs.

3. Avoidance of swimming or wading in fresh water streams or ponds and avoidance of drinking from irrigation ditches frequented by rats.

4. Proper veterinary care of sick dogs and cats; these animals should not be fondled, and contact with their urine should be especially avoided.

5. Active immunization of individuals in localities where exposure to infection exists, if such a measure be possible.

6. As the infection appears to be transmitted through the medium of the urine and feces, sterilization of these discharges from those sick with the disease should be practiced. Hoagland, Harris and Chinen[42] in 1943 state that when a patient with Weil's disease is being treated, the usual contagious disease precautions should be taken by the ward personnel. The patient should be isolated and should wash his hands with 1% cresol solution after each urination. The urine should be disinfected before it is disposed of. They also suggest that it may be possible to end the urinary carrier state by giving mandelic acid and urine acidifying drugs.

7. Scrupulous care to prevent food from being contaminated by the discharges of rats and mice also is of great importance.

8. Fish workers, sewer workers, and workers in damp mines, should take care to prevent or protect abrasions of the skin which favor infections.

9. Since fish remnants especially attract rats, and since the spirochetes live in the slimy water, care should be taken to remove all offal at the end of each day's work. The floors, benches and tables of fish warehouses should be vigorously hosed with water and thereafter treated with a suitable disinfectant. One worker has found a hyperchlorite solution in a dilution of 1:4000 has a lethal effect on leptospiras.

10. Laboratory workers must take precautions in handling infected animals and wear gloves.

Treatment. Soon after the cause of Weil's disease was established, a search for protective antibodies in convalescent patients was begun. The Japanese, thanks to the work of Inada,[44] were the first to demonstrate such antibodies and to use these agents in therapy. By 1916, both horse serum and goat serum containing antibodies against *L. icterohæmorrhagiæ* had been produced. A few years later, a curative rabbit serum was developed. The most widely used sera came from horses whose blood has been raised to an agglutinating titer of 1:100,000 or higher against *L. icterohæmorrhagiæ* and *L. canicola*. Inada[43] fixes the dose at approximately 60 cc. of such serum. Walch-Sorgdrager,[105] Griffith,[35] and Inada indicate that this form of therapy is effective in lowering the mortality rate, especially if given in the first 6 days of the disease. These represent reports from Holland, England, and Japan. Comparable favorable reports have also come from France and Germany. In Japan alone, Inada reports that the mortality rate in one group of cases was lowered from 30.6 to 18.3%. Strong[95] recommends that the serum be given intravenously at intervals of several hours for at least 3 or 4 days. Twenty cc. at least should be used for each injection. Tokuyama[99] in 1939 studied 9 patients in Hawaii, 6 of whom were treated by intravenous injections of immune serum. Four patients recovered and 2 died. Of the 3 untreated patients, 2 died. There was little evidence that the treatment had any effect, although in 2 instances the infection was followed by general improvement. Schüffner[85] points out that if the serum is not given until jaundice appears, its efficacy is very greatly reduced. D'Silva[21] in 1942 tried antileptospira serum in 10 cases and his results were very disappointing. He gave doses of from 40 to 60 cc. intravenously. The failures might have been due to the difficulty in obtaining a polyvalent and potent antiserum against the

different local stains of leptospira. Ashe[3] concludes from his studies that the treatment of choice is immune serum. As yet, the American drug houses have done nothing about preparing such sera, nor can they be expected to do so until city and state laboratories make available the necessary diagnostic procedures, and until the true incidence of the disease in the United States becomes known.

Larson[55] in 1943 showed that serum from patients convalescent from Weil's disease and immune rabbit serum and plasma prevented the death of young white mice infected with *L. icterohæmorrhagiæ*. He also showed that the effect of these materials is marked if administered on or before the 4th day after injection. Ashe[3] in 1941 reported the first serum treated case in this country. He gave 500 cc. of whole blood from a person who was convalescing from Weil's disease to a patient who had the active disease. The blood was given on the 9th day of the disease, at which time the patient had been completely anuric for a period of 30 hours. Within 6 hours after therapy he began to void, and improved steadily thereafter. No antibodies were found in the patient's serum before therapy, but they were abundant thereafter. Gaines[29] gave 30 cc. (a small amount) of convalescent blood intramuscularly to 1 patient, but complete identification of the infecting spirochete was not made in the recipient. Walch-Sorgdrager[105] show that, while the severity of symptoms and the mortality are favorably affected by the use of immune serum, the duration of the febrile period is not altered. When serum has not been effective, it is felt by many that an adequate dose was not given. Clapper and Meyers[12] in 1943 report that these immunotransfusions may be of value in treatment and a more extended trial in their use is certainly justified. Ashe mentions that, until immune sera appear on the American market, convalescent serum or whole blood transfusions should be used when possible.

Soon after the recognition of *L. icterohæmorrhagiæ* as the etiologic agent in Weil's disease, many attempts were made to kill the spirochete *in vivo* with specific arsenicals such as salvarsan and neoarsphenamine, but without success. Furthermore, there is a real danger in administering certain toxic substances in the presence of much liver and kidney disease. Neoarsphenamine has been used by some workers with reports of fairly good results.

Sazerac and Nakamura[84] in 1927 used soluble bismuth preparations, such as sodium bismuth tartrate given intravenously, and have shown it to be effective and non-toxic in guinea pigs. In Germany, a few human cases have been treated with soluble and colloidal bismuth compounds with reported success. There is still dispute as to whether the bismuth is bactericidal or bacteriostatic, or whether it merely stimulates the normal body defense mechanism. Uhlenhuth and Seiffert[101] in 1929 used soluble colloidal bismuth yatren compound and reported good results. Antimony compounds have proven useless.

Because certain soaps and resins are known to dissolve the spirochete *in vitro*, sodium ricinoleate has been used experimentally in animals with some beneficial results, but there are no reports in the literature that these agents were ever useful in man.

Ashe[3] reports the use of sulfanilamide as useless. He treated one of his cases with large doses of sulfanilamide (10 gm. daily for 3 days) during the bacteremic first stage, and it did not alter the number of organisms in the blood stream; nor did it in any way influence the course of the disease. Walch-Sorgdrager[105] used prontosil in the Netherlands without benefit.

Senekjie[87] also reports that he used the sulfa drugs without any apparent effect. It was only good to help combat secondary infections.

Since hyperimmune horse serum and convalescent serum are not available and since the diagnosis is usually made late during the course of an infection, it is obvious that specific treatment is not practical. The treatment is, therefore, chiefly symptomatic. The basic principles should be: ensuring rest, quickly eliminating the toxins, and "anticipatory therapy," *i. e.*, preventing the onset of the grave symptoms and sequelæ, such as hemorrhages, cardiac failure, toxemia, cholemia, anuria, persistent hiccough and vomiting, hyperpyrexia, parotitis and cystitis. A brief of the accepted supportive treatment is:

1. *Rest.* Absolute rest in bed is essential in view of the possibility of sudden heart failure due to cardiac musculature being involved during the acute and convalescent stages.

2. *Sedation.* Early administration of sedatives was found necessary owing to the intensity of muscular pains and restlessness.

3. *Elimination.* Elimination of toxins by diuretics and diaphoretics and by purgation. D'Silva[21] recommends the use of camphor as a diaphoretic. He also advises the use of urotropine since it acts primarily as a biliary and urinary antiseptic and secondarily perhaps as a spirocheticide against the leptospiras, which are believed to lodge inside such organs as the liver, gall bladder and kidneys. Moreover, urotropin, being excreted by the meninges, proved a valuable remedy in the meningeal type of the disease. It also prevented subsequent bacilluria and parotitis. "Catagone" by intravenous injection was tried with great success in 10 cases in place of urotropin.

4. High carbohydrate, protein, vitamin diet to support the liver. White and Prevost[108] advise the use of liver extract along with the usual supportive measures.

5. Calcium gluconate given parenterally.

6. *Fluids* must be adequate. They may be administered by mouth, hypodermoclysis, or by intravenous infusion. Saline and glucose infusions should be given frequently.

7. Small *transfusions* are helpful in many cases.

8. If kidney failure starts to occur, increase the amount of *glucose* being given, give caffeine derivatives in moderately large doses, use diathermy and hot packs over the kidney regions. Mercurial diuretics are contraindicated.

9. Cardiac stimulants are indicated when there is derangement of cardiac function.

10. During convalescence, various tonics, vitamins and iron should be given.

Prognosis. According to Ashe,[3] the prognosis is dependent upon the following factors: (1) age of the patient; (2) the presence or absence of jaundice; (3) the degree of renal failure; (4) the function of the heart; (5) the extent of the hemorrhagic diathesis.

Weil's disease is practically unknown in infants, and is rare in children. The mortality rate increases rapidly with advancing age. According to Walch-Sorgdrager,[105] in the fatal cases, death usually occurs between the 9th and the 16th day. Inada[44] reports the Japanese fatality rate in untreated cases as being 30%. Strong[95] mentions that the mortality rate has varied in different countries from 4 to 32% in Europe to 48% in certain Japanese outbreaks. The virulence of the outbreak has varied in different countries, and a varying susceptibility in individuals has been demon-

strated. In larger series of cases in Europe, the mortality rate ranges from 11.9% (some of these were apparently serum-treated) to 60% in the most severe epidemics. In the United States, the mortality rate[3] to date is about 30%. Senekjie[87] in 1944 reports a mortality rate of 16.6% in his cases. The mortality in the Andaman Islands has been reported as 18.7% and in the Isle of Syra (Greece) as 12%. In the sugar cane cutters of Queensland, a morbidity of 18% and a mortality of about 4% was reported.

Walch-Sorgdrager reported the following series from Holland:

	Died	Fatality rate %
Out of 11 persons aged 1 to 10	0	0
Out of 210 persons aged 10 to 40	15	7.1
Out of 49 persons aged 40 to 60	12	24.0
Out of 15 persons aged 60 or over	9	60.0
Out of 85 persons of unknown age	8	9.4
Totals, 370 cases	44	11.9

Of the 370 cases, approximately 50% were jaundiced. The number of serum treated cases is not stated. Schüffner[85] in 1934, also reporting cases from Holland, found 452 cases in 10 years, among whom there were 46 deaths, or 10.2%. In his cases with jaundice, from 1924 to 1931, a mortality of 32% occurred, and in 1932 to 1933 a mortality of 16%. He thought that the lower mortality in the later years was due to the lessened virulence of the disease and in part to the effects of serum therapy, the use of which has been considerably extended in Holland. Schüffner believes no one dies of Weil's disease unless suffering from jaundice, and that Weil's disease without jaundice is as harmless as any other leptospirosis which never shows jaundice in its course, like "swamp fever," or "seven-day fever." Walch-Sorgdrager is the only worker to report a death which occurred without jaundice. He reports one instance of this nature. The intensity of the jaundice when present is probably not nearly as significant as the patient's age, although icteric indices of over 200 should always be looked upon gravely.

In the typhoidal, uremic, and meningeal forms, the prognosis is usually bad. It is especially grave when the cerebrospinal fluid is under pressure and contains an excess of albumin and leptospiras in large numbers. Nevertheless, death does not always occur. Murgatroyd[74] in 1939 reported a recovery from a case of meningitis in which the leptospiras were recovered from the cerebrospinal fluid months after the onset of the disease.

The degree of renal failure as indicated by the urine output and the degree of urea retention, is important for prognosis. Oliguria and a high blood urea are usually serious, and anuria is always a grave sign. A high blood urea without oliguria is usually not a serious sign.

In most cases, the cardiovascular system responds well to the disease; but occasionally a very rapid pulse, out of proportion to the temperature and associated with a relatively low blood pressure, is encountered. Pronounced and long-continued bradycardia is of serious significance.

Usually, the hemorrhagic diathesis is not of significance, but rarely, in the very ill older individuals, bleeding from the respiratory, gastro-intestinal, and urinary tracts may become so serious as to become a definite hazard to life.

In Japan, it has been definitely shown that early diagnosis and therapy can materially lower the mortality rate in all groups.

Complications. Many complications may occur during and soon after the course of the disease. Perhaps the two most common complications are iridocyclitis and optic neuritis. Reports of iridocyclitis are fairly common in the German literature, and one worker observed it in 44% of his cases including the mild ones. In the Netherlands the figure is given as 10% and is considered a minimum.[105] Walch-Sorgdrager could find no cases without recovery. Optic neuritis is apparently less common, and is not of much importance. Rathbun and Waghelstein[78] mention that iritis or iridocyclitis is present in from 10 to 44% of patients. Other complications reported by these men are meningitis with complete paralysis and skin eruptions which occur in 10 to 36% of patients.

St. Amant[90] in 1943 mentions certain nervous complications that may occur during the course of the disease:

1. Cerebral symptoms, such as headache, restlessness, dizziness, and bradyphrenia, due to the general infection are very common.
2. True meningitis with changes in the spinal fluid and occasionally with spirochetes in the spinal fluid is also fairly common. Meningitis may be the only manifestation of Weil's disease.
3. Symptoms indicating an affection of the nerve parenchyma, which in milder cases (reduced or abolished tendon reflexes, possibly slight paresis) may conceivably result directly from the meningitis as a spread to the nerve parenchyma.
4. In rare cases, complications indicate a more severe affection of the cerebral parenchyma which is not due to a spread from meningitis but is a complication *per se*. It is probable that the spirochetes may tend to attack the nerve parenchyma, in view of the fact that complications involving the peripheral nerves are not uncommon.

A few rare complications have been described, which may be fatal: such as myocarditis, acute vegetative endocarditis in which lepsospiras are found, parotitis, and terminal purulent meningitis. Inada[44] reports a case where the fatal complication was a purulent meningitis. Severe hemorrhages and multiple liver abscesses are also rare complications of Weil's disease.

Summary. A brief review of Weil's disease as it occurs in foreign countries is presented with a more detailed review of the disease as it exists in America and Great Britain, placing special emphasis on the more recent findings and reports.

Judging from the American literature, Weil's disease is probably not rare in this country; and since, untreated, it has a mortality rate of about 30% in jaundiced cases, there is every justification in calling attention to this 54 year old disease. The physician should be alert to confirm or to exclude the diagnosis of leptospirosis on encountering an acute febrile illness even in patients without jaundice, in one whose work is likely to involve exposure to rat-contaminated surfaces, particularly if the illness resembles influenza, pneumonia, or enteric fever, or if renal insufficiency or a hemorrhagic tendency is present. Physicians should realize that leptospirosis is a protean infectious disease with symptoms sometimes so mild that diagnosis is difficult except by bacteriologic means. The more frequent recognition and diagnosis of Weil's disease would appear to depend on a wider appreciation of its prevalence, a greater familiarity with its clinical symptomatology, particularly that of the initial pre-icteric stage, and a more frequent use of laboratory tests of proved diagnostic value at appropriate stages of the infection. Many authors advise making Weil's disease a reportable

infection here in the United States, because the condition seems to be more prevalent than the reported figures would indicate.

A general recognition of the disease in the United States is desirable, because therapy is simple and effective. Until the true incidence and importance of the disease is realized by American physicians, the much-to-be-desired goal will not be obtained.

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NEUROLOGY AND PSYCHIATRY

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RELATIONSHIP AND FUNCTION OF THE PYRAMIDAL TRACT

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The prevalent teaching regarding the voluntary motor system is summarized by Tilney and Riley[50] (1938). "The impulses of this volitional control arise in a certain area of the cerebral cortex known as the Rolandic or motor area. This portion of the brain contains many large pyramidal

* Now on active service.

cells whose axones, the pyramidal fibers, eventually bring the impulses of volitional control to the motor cells of the ventral gray column. There is also a type of cortical control which exerts an inhibitory influence upon the tone of the muscles. . . . . When the connection between cortex and ventral horn cells is interrupted, the patient not only loses the power of volitional control of the affected muscles but the muscles themselves become unusually contracted. . . . . Such hypertonicity or spasticity is accompanied by an increase in reflexes of the affected part."

The following assumptions have been made regarding the pyramidal or corticospinal tract: (1) It originates in the giant Betz cells of the motor area (area gigantopyramidalis, Area 4 of Brodmann, Area FB of Economo and Koskinas). (2) It terminates in synapses with anterior horn cells. (3) It is *the* upper motor neuron and is the anatomic substratum for all voluntary movement. (4) It is not only responsible for movement but is also an inhibitory mechanism, exercising control over the lower motor neuron. A lesion of the pyramidal tract therefore gives rise to (*a*) spastic paralysis, (*b*) hyperactive reflexes and (*c*) pathologic reflexes.

A large body of experimental evidence is now available which casts considerable doubt upon these assumptions.

Origin. In 1874 Betz,[3] a Russian histologist, described the giant pyramidal cells in the fifth layer of the precentral cortex. The idea that the pyramidal tract has its origin in these giant cells has been impressed upon neurologic literature largely as a result of 3 investigations conducted in England during the early portion of this century. These investigations were the electrical stimulation experiments of Grünbaum and Sherrington[25] (1903) on the cortex of the higher apes, the cytoarchitectural descriptions of Campbell[6] (1905), and the studies of retrograde degeneration following spinal cord lesions by Holmes and Page May[29] (1909). Campbell, following the early experiments of Grünbaum and Sherrington on the motor area of higher apes, concluded that the Betz cells represented the true motor elements of the cortex. He believed that the area of Betz cell distribution (his "precentral area") coincided exactly with the motor area as delimited by Grünbaum and Sherrington. It was only after the publication of Campbell's work that Leyton (Grünbaum) and Sherrington's final study appeared[36] (1916), enlarging their original "motor area" anteriorly. They stated at this time that the electrically excitable cortex extends in front of Campbell's precentral area (Brodmann's Area 4) and into his intermediate precentral area (Brodmann's Area 6). Four years after Campbell's publication, the studies of Holmes and Page May on "the exact origin of the pyramidal tract" appeared. These investigations found that in all types of mammals including man, hemisection of the spinal cored resulted in chromatolysis and further degenerative changes in the Betz cells; such changes were noticed in no other cortical cells. They therefore concluded that all pyramidal fibers arose from these giant cells. For the next 30 years this evidence became for most the indisputable proof of the origin of the pyramidal tract.

Specificity of the Betz Cell. Walshe[54] (1942) raises the question as to whether the Betz cell is truly a specific morphologic unit. He points out that different investigators have given widely different dimensions for these cells. If all of these dimensions were to be included, the cells would vary in size from 30 μ long and 12 μ broad to 120 μ long and 60 μ broad. Economo and Koskinas[12] have defined 5 different types of pyramidal cells in the cortex: (1) small pyramidal cells, varying in height (H) from 10 to 15 μ and in breadth at the base (B) from 7 to 10 μ; (2) middle-size

pyramidal cells $\frac{H}{B} = \frac{20 - 30}{10 - 20}\ \mu$; (3) large pyramidal cells $\frac{H}{B} = \frac{30 - 50}{15 - 20}\ \mu$; (4) giant pyramidal cells $\frac{H}{B} = \frac{50 - 60}{25}\ \mu$; and (5) Betz giant pyramidal cells $\frac{H}{B} = \frac{60 - 120}{40 - 60}\ \mu$. According to Economo and Koskinas, many transitional forms exist between these various types of pyramidal cells. Lassek[32] (1941) has made a careful study of the size of the large pyramidal cells in the fifth layer of Area 4, the cells being measured in square microns with a planimeter. As did Economo and Koskinas, Lassek concludes that there is great variability in the size of these cells. Of cells measuring between 900 and 4100 square microns, there is a gradual decrease in number from the smallest to the largest. The average size of the cell is largest in the upper third and smallest in the lower third. Walshe concludes, "Classification thus provides us with three categories of large pyramidal cell—Betz cell, simple giant cell and large pyramidal cell—but it seems clear that every possible transition form between the members of this conventional grouping is to be seen, not only in the adult cortex as reported by Economo and Koskinas, but also in the infant cortex as reported by Conel (1942). At one extreme we have the Betz cell with its numerous large Nissl granules, at the other the slenderer large pyramidal cell which only exceptionally contains distinct Nissl granules, but the series is continuous, and we can no longer accord the Betz cell the exclusive position we have hitherto given it as a specific entity with functions exclusive to itself. The Betz cell is no more than the largest and most massive member of the large group of pyramidal cells. . . . . For purposes of description, classification is necessary, but having once made our groups, we are too ready to assume that we have discovered essential qualitative distinctions that may have no reality in nature."

Just as the size of the Betz cell is not clearly defined, neither is its area of distribution. Economo and Koskinas state that the posterior boundary of Area FA (Area gigantopyramidalis) is in the anterior wall of the fissure of Rolando, about 2 mm. from the floor of the fissure and the medial limits are in the paracentral lobule. The anterior limit and the lower limit near the fissure of Sylvius, however, are not readily demarcated. The largest Betz cells are found in the medial aspect of the area, *i. e.*, in the posterior portion of the paracentral lobule (leg area). Anteriorly and in the direction of the fissure of Sylvius, the size of the cells progressively diminishes. The cells, characteristically occurring in clusters, are not even distributed in Area 4. The simple giant cells and particularly the large pyramidal cells of Economo and Koskinas, however, extend well into Area FB (Area 6 of Brodmann). In the lowest portion of Leyton and Sherrington's electrically excitable cortex, no Betz cells which fit Economo and Koskinas' description are to be found. Betz cells are also described in the postcentral Areas PA, PB, and PC and PD of the parietal lobe.

Levin and Bradford,[35] repeating the retrograde cell degeneration studies of Holmes and Page May on monkeys, have attempted to solve the problem by enlarging the scope of the definition of the term Betz cell. After sectioning the pyramidal tract and studying the pyramidal cells of the cortex, the bulk of the retrograde degeneration is seen in Area 4 of Brodmann. Considerable degeneration, however, is also present in Areas 3, 1, 2 and 5 of the parietal lobes. Furthermore, it is not confined to the Betz giant cells, inasmuch as large and medium-sized pyramidal cells are also affected. They therefore suggest that the term "Betz cell" be modified to include cells of any size giving rise to corticospinal fibers.

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Relationship of Pyramidal Tract and Betz Cell. As noted above, retrograde cell changes following pyramidal tract section are noted not only in Area 4 but also in Areas 3, 1, 2 and 5 of the parietal lobe. Levin and Bradford expressed the opinion that almost 20% of the pyramidal fibers (in macaca radiata) arise in the parietal lobe, the remainder arising in Area 4. Peele[45a] (1942) also states that the giant pyramidal cells of Areas 2 and 5b contribute to the corticospinal system. Marchi degeneration has been noted in the spinal cord following ablation of Area 6 (Kennard[30a]), evidence that this area also gives rise to corticospinal fibers. Levin[34] explains this degeneration on the basis of "heterotopic Betz cells" in Area 6. More recently (1944) Welch and Kennard[55] have pointed out that pyramidal tract degeneration differs markedly in animals in which the motor areas have been removed from those in which the hemisphere has been removed. "Thus, in the medullary pyramid there was complete degeneration of all fibers when one hemisphere had been removed, but following extirpation of Areas 4 and 6, the degeneration was only moderate. When the postcentral gyrus was added to the motor areas, the degree of degeneration lay between the two above extremes. In the dorsolateral tract of the cord removal of Areas 4 and 6 caused relatively slight loss of active fibers and even hemispherectomy did not produce complete degeneration. The existence within the 'pyramidal tract' of the cord of extrapyramidal fibers with cells of origin below the cortical level is thus indicated by the difference between total number of fibers showing degeneration in the tracts at medullary and spinal levels in the same animal."

The crowning blow to the work of Holmes and Page May has been dealt by Lassek[32,33] in a series of papers beginning in 1939, correlating counts of pyramidal tract fibers with counts of Betz cells. It was first shown that there are somewhat over 1,000,000 fibers in the human pyramidal tract, 61% of which are myelinated (Lassek and Rasmussen[33]). Most of the fibers are of small caliber, indicating that the bundle as a whole conducts slowly. In the past many of these fibers have been missed, largely because the main dependence has been on the Marchi stain which is ineffective in revealing small, unmyelinated fibers. Lassek has utilized the Davenport protargol method. Counts were then made of all of the large pyramidal cells in Area 4 from 900 to 4100 square microns in area. Approximately 34,000 cells were counted in the human. Thus it follows that the Betz cells can contribute but from 2 to 3% of the fibers in the pyramidal tract. Lassek expressed the belief that inasmuch as the large pyramidal cells of Area 4 are but a fraction of the total number of fibers of the pyramidal tract and the large caliber fibers in the pyramidal tract are also in the minority, these cells give rise to the rapid impulses carried by large caliber fibers. Approximately the same relationship exists between giant cell and pyramidal fibers in the rhesus monkey and in the spider monkey (*Atelus ater*). In the latter there appears to be no correlation between the number of these cells in various portions of the motor region and the ability to perform skilled movements. For, whereas it uses its thumbless hand poorly and has great dexterity with its tail, it has a higher percentage of giant cells in the lower third of Area 4 (arm area) than either the rhesus monkey or man.

Lassek has also described the changes in the histologic appearance of the pyramidal tract from infancy to old age. While apparently all of the axons are present during the first few months, they are small, delicate, uniform in caliber, crowded and possibly of a different chemical nature than when mature. At 8 months, about the time that myelinization

starts, a few axons accelerate in growth, while the remainder remain stationary. Presumably these are to become the large, myelinated axons of the adult. At 2 years, the pyramidal tract, while smaller, resembles that of an adult. In senility there is a decrease in the number and diameter of fibers. While myelinization has been stressed as the determining factor in the onset of function, Lassek expresses the belief that morphologic and chemical changes in the axons are also of importance.

The application of the method of retrograde degeneration has been brought to task by Lassek. He points out that not only do many pyramidal tract fibers remain intact above the site of the lesion but also that small nerve cells do not show chromatolysis. The large motor cells are probably the only ones in which changes may be noted following tract section. While Betz cells undergo shrinkage and loss of Nissl substance following pyramidal tract section, there is no retrograde degeneration of pyramidal neurones. This leads Lassek to the conclusion that the Nissl substance is not responsible for the nutrition and metabolism of the axon and shows that the retrograde method, employing the Nissl stain, does not prove that the giant cells give sole origin to pyramidal fibers.

Termination. It has long been taught that the pyramidal tract terminates directly upon the anterior horn cell (Flechsig,[15] 1876). A good deal of evidence had accumulated, even in the later part of the 19th century, that such was not the case. Both von Monakow[44] (1884) and Pick[47] (1898) had expressed the view that an intercalated neurone was present, its cell body lying in the dorsal portion of the spinal gray matter. Sharpey-Schafer, Lewandowsky and Rothman were all unable to detect pyramidal fibers ending around anterior horn cells. The differences in opinion may be attributed largely to the unsatisfactory staining methods that were available at the time.

Hoff[27] has employed the method of bouton degeneration in an effort to solve the enigma. It has long been known that synapses of axon terminals with cells in the spinal gray matter are characterized by the presence of Endfüsse or *bouton terminaux*, small looplike structures in close proximity to the cell body. Hoff has shown that these boutons undergo a characteristic degeneration following section of the axon to which they are endings. First, they swell and thicken, in the course of 3 days becoming enlarged granular masses. In from 4 to 6 days the boutons have completely disintegrated. Using this method, Hoff and Hoff[28] have studied the spinal gray matter following removal of the cortical motor areas. Following unilateral extirpation of Area 4, bouton degeneration for the most part (80 to 90%) occurs in the intermediate zone of the contralateral gray matter, while but a minority terminates in the ventral horn. They conclude that the pyramidal tract ends chiefly around internuncial cells in the intermediate region. They also note that following dorsal root section, the area of bouton degeneration overlaps that which is seen with cortical ablations. This confirms the statement of Ariens Kappers that corticospinal fibers terminate mainly on cells which are in direct contact with afferent, rather than efferent, fibers.

Using electrophysiologic methods, Lloyd[38] has arrived at somewhat the same conclusion as that of Hoff in regard to the termination of the pyramidal tract. The animals were first decerebrated at the collicular level. Stimulating electrodes were inserted into the pyramidal tract of decerebrate cats at the level of the trapezoid body. A lesion was made caudal to these electrodes, severing all descending and ascending pathways except the pyramidal tract. By means of micro-electrodes placed along

the pyramidal tract and in the gray substance of the spinal cord, it was possible to study the speed of impulses carried in the tract and to determine the number and location of synapses. The most rapid conducting fibers of the pyramidal tract had a velocity between 60 and 65 meters per second. Many slower conducting axons were also present; dispersion of a volley, synchronous at the medullary level, continued to produce a discharge of pyramidal impulses lasting many milliseconds. This closely parallels Lassek's description of the variation in size of pyramidal tract fibers—the larger, fast-conducting fibers being outnumbered by the smaller, slower conducting ones. Small nuclear elements, in close proximity with the pyramidal tract (external basilar region), appeared to constitute the initial internuncial relays. A second internuncial relay appeared to exist in the intermediate gray region (intermediate gray nucleus of Cajal) which synapses with the motoneurone (anterior horn cell). It also appeared likely that pyramidal fibers have synapses with the solitary large cells of the dorsal horn, sensory in character. All the effects of stimulation were of an excitatory nature. No evidence was found that the pyramidal tract is of any importance in producing inhibition.

It can therefore be concluded that the pyramidal tract is in a position not only to influence the motor neuron but also the sensory impulses entering the cord over the dorsal roots.

Consideration of Pyramidal Tract Function From Lesions at Decussation and in Spinal Cord. The assumption that spastic paralysis, hyperreflexia and pathologic reflexes follow lesions of the pyramidal tract has been so deeply installed in neurologic thinking that these findings are often referred to as "pyramidal tract signs." These suppositions are based largely on clinical material, in which lesions rarely, if ever, are confined purely to the pyramidal or corticospinal system. By definition the pyramidal tract contains those fibers that pass through the medullary pyramids. It is only in this location that the fibers exist as a segregated unit. The pyramidal tracts may be approached surgically through an incision in the anterior midline of the neck after removing a portion of the basiocciput. Recently such experiments have been reported by Marshall[39] and by Tower[51a] in the cat, and by Tower[51b] in the monkey.

Marshall stated that most of his cats had little difficulty in walking following pyramid section, even on the second postoperative day. The animals, in general, suffered less impairment than those in which the motor areas have been removed. Marshall described an "initial symptomatology," which includes (1) diminished or absent contact placing reactions, (2) reduced visual placing reaction, (3) difficulties in walking a ladder or narrow tract, (4) delayed hopping reactions, (5) increased resistance to passive flexion, with the animal suspended in a sling, (6) diminished resistance to passive extension, (7) spontaneous postural abnormalities, (8) non-correction of abnormal postures imposed on the feet, (9) occasional transient staggering, (10) a certain stiffness in gait, (11) a heavy and awkward landing after jumping down from a height and (12) reduced activity and slowness in motion. A degree of recovery took place from all of the symptoms; sometimes it was complete. "*There was no constant set of symptoms remaining over at the end of the period of observation of 2 to 3 weeks.*"

Tower was unable to discover any spasticity in cats in which the pyramids had been sectioned. In her study of pyramidal lesions in the monkey, she described the presence of a contralateral "hypotonic paresis" (quantitatively less than a "flaccid paralysis"). This paresis affected all so-

matic function, though not equally, and some visceral function. Its outstanding features were diminished muscle tone; diminished cutaneous reflexes; slow, full tendon reflexes restricted to the muscles stimulated; lowered skin temperature; defective initiation and execution of all performance by skeletal musculature with elimination of non-stereotyped components, and elimination of all discrete usage of the digits. In general, the threshold of reflexes was raised and they were weak and sluggish. The hypotonia was most noticeable in the hip and shoulder musculature. Following bilateral section, the hypotonia was also marked in the musculature of the neck, back and thorax—"axial hypotonia." The animal with bilateral pyramidal section, unable to compensate with a healthy side as the animal with unilateral section, developed a greater range of movement than was seen in the paretic extremity of the latter. This movement was highly volitional and purposive. It was carried out slowly and laboriously; ready fatigability was present.

Tower draws the following conclusions regarding the function of the pyramidal tract: "It is organized in complexity to match virtually the full range of activity, from simple tonic functions wherein it merely assists, to complicated performances which are primarily its responsibility. Although traditionally, the pyramidal system has been considered 'the voluntary motor pathway,' this is too sweeping. An impressive capacity for voluntary movement survives pyramid section, especially if the lesion be bilateral, forcing the issue. Conversely, some activities eliminated by pyramidal lesion, for example the contact placing reactions, must be considered, if not involuntary, at least highly automatic. By virtue of its tonic action on the spinal cord, pyramidal function must assist all somatic motor activity, if not, indeed, all motor activity of the waking animal, at whatever level initiated, even the spinal reflex level, without regard for the voluntary or automatic quality of particular acts. As the agent of lability, however, the pyramidal tract makes a unique contribution to total performance. Together, the all-pervading, and the discriminating qualities of corticospinal action afford the cerebral cortex that influence in virtually all realms of final motor action, and that minuteness of control which determine its effectiveness as an agent of choice. In this service of choice the pyramidal tract is unquestionably the outstanding, though not the exclusive, voluntary motor pathway."

Cannon, Beaton and Ranson[7] have recently reported their results on the interruption of the lateral corticospinal tract in the monkey. Additional descending fibers than those of the pyramidal tract, however, were interrupted. In spite of this, the paresis was characterized by hypotonicity, hypoactive reflexes and the absence of clonus—much the same findings as in Tower's monkeys. The paresis was more prominent in the upper than the lower extremity and more extreme in the distal rather than the proximal musculature.

Putnam's[48] treatment for paralysis agitans by section of the lateral pyramidal tract in the cord has given information regarding the lesion in the human. While the results are confused by the presence of additional neurologic deficit and the probable involvement of other descending pathways, the patients appear to suffer less disability than Tower's monkeys and retain discrete digital movement. This may be due to lack of involvement of all pyramidal fibers in the cord section. In contrast, to Tower's monkeys, some of the patients have exhibited slight spasticity and hyperreflexia.

All of these investigators agree that pyramidal section does not result

in a lasting spastic paralysis. It follows, then, that the enduring spasticity and paralysis so frequently observed in the human following a capsular thrombosis, for instance, is not due solely to interruption of corticospinal fibers as has been commonly attributed.

Pyramidal Tract and Cortex: "Motor Area," "Premotor Area," "Suppressor Areas, Parietal Lobe; Relationship of Basal Ganglia. "Motor area," "Area 4 of Brodmann," and "area pyramidalis" have been used as synonymous designations. From the early cytoarchitectonics of Campbell, attempts have been made to define motor cortex histologically rather than physiologically. Obviously the terms "motor area" or "motor cortex" only have meaning in terms of motor function. The attempt to force them into a histologically more or less well-defined area, plus the previously mentioned attempt to restrict the origin of the pyramidal tract to a specific type of cell in the fifth layer of this area has resulted in an overly simplified picture of motor function.

The physiologic methods at our disposal for the study of cortical motor function include (*a*) stimulation experiments, either mechanical, chemical or electrical, the latter being preferred, and (*b*) ablation experiments.

Cortical Electrical Stimulation. The early stimulation experiments of Fritsch and Hitzig[19] (1870), Ferrier[14] (1873), and Beevor and Horsley[2] established the existence of a motor area in a variety of mammalian cortices. The later, more refined studies of Leyton and Sherrington[36] (1917) on the cortex of chimpanzee, orang and gorilla further elaborated the various components of the cortical motor area. As was noted previously, in their earlier publication (1903), the electrically excitable cortex was limited to Area 4, or Campbell's precentral area. In the 1917 publication, however, "The motor field's boundary seems to lie, especially in its lower two-thirds, farther forward than does Campbell's precentral area. The anterior border as determined by faradization is, however, not a sharp one, and its situation seems to vary somewhat from specimen to specimen. As placed by us, it certainly appears to lie for the most part in the intermediate precentral area of Campbell. Opposite the 'arm area' it lies not far behind the anterior border of the intermediate precentral area, but opposite the 'leg area' it lies very much further behind the anterior limit of the intermediate precentral area, although in front of the anterior limit of the pure precentral area of Campbell." Thus Leyton and Sherrington include a portion of Area 6 in their "motor area."

Modern studies of the electrically excitable cortex of the human include those of Foerster[16] (1936), Penfield and Boldrey[46] (1937) and Scarff[49] (1940).

Foerster, in plotting the motor points of the cortex, found that both Area 4 and Area 6aα (using the Vogts' terminology) respond to electrical stimulation by the isolated movements of a part of the body or of a single segment of the extremities. But to obtain these effects from Area 6aα a considerably stronger stimulus is needed than in Area 4. Following undercutting the cortex between this area and Area 4 the isolated movements are abolished. Strong faradic stimulation of Area 6aβ (the rostral portion of Area 6) produced complex mass movements on the contralateral half of the body. Foerster has called this area (6aβ) the "frontal adversive field," because of the production of adversive movements, that is turning of the head, eyes, and trunk in the opposite direction. When Area 6aα was rendered impotent in the production of isolated movements by undercutting between it and Area 4, it responded with the same type of mass movement as did Area 6aβ. Stimulation of Area 6aα of the Vogts, lying rostral to the "face area" of Area 4, resulted in sustained,

rhythmic and coördinated movements of lips, tongue, mandible, pharynx and larynx. Isolated movements were also produced by stimulation of the postcentral gyrus (Areas 3-1-2 of the parietal lobe). As in the case of Area 6aα, these movements were produced at a higher threshold than those from Area 4 and were abolished by undercutting them between them and Area 4. Stimulation of Area 5, the superior parietal lobe, and of Area 22 in the temporal lobe gave rise to the same mass movements as noted following stimulation of Area 6aβ. Foerster concluded that isolated movement from Area 6aα and Areas 3-1-2 "depend upon the integrity of Area 4 and its motor pathway, the pyramidal tract. So we can say that the Area 4, the *area pyramidalis*, is the specific area for isolated innervations." The more complex movements arising from Areas 6aβ, 5 and 22, "extrapyramidal cortical areas," descend along other, extrapyramidal, pathways.

Penfield and Boldrey (1937) have made some modifications in the cortical motor points of Foerster. "It is seen that toes begin at the top [of the fissure of Rolando] and the members follow in order as though representing a man hung upside down, but that thumb is followed by the head as though the head and neck were erect and not inverted." The areas for the thumb and lips was "very large," for the trunk "quite small," and for the legs and head "very small." Discrete responses were obtained from the postcentral gyrus, though less frequently than from the precentral gyrus (Area 4). They failed to verify the presence of motor responses described by Foerster in Areas 6aβ, 5 and 22 and feel that these may have been epileptiform discharges. "Thus our results from stimulation resemble those of Grünbaum and Sherrington in the chimpanzee except that they got no responses from the postcentral gyrus." Recently (1940), it should be added, Hines[26b] reports a number of motor points in the postcentral gyrus of the chimpanzee. Furthermore, Peele[45b] (1944) states that it is possible in the monkey to delimit Areas 5 and 7 in the posterior portion of the parietal lobe from Areas 3, 1 and 2 in the anterior portion or postcentral gyrus, according to the type of movement elicited and the threshold. Stimulation of Areas 3-1-2 resulted in flexion movements while stimulation of Areas 5 and 7 resulted in elevation of the contralateral shoulder and protraction of the entire upper limb.

Scarff[49] (1940) has criticized the view that the human motor area is similar to that of the chimpanzee. He has expressed the belief, on the basis of electrical stimulation, that the motor strip in man has migrated upwards. "The primary motor area for the upper extremity commonly extends upward on the lateral surface of the cerebral hemisphere as far as its superior mesial border, while the leg, as a rule, is represented only on the mesial surface of the cerebrum." This may explain the infrequency of movements in the lower extremities and the small area allotted to the leg area by Penfield and Boldrey.[46] These investigators did not stimulate the mesial surface of the hemisphere. This upward "migration" of the motor strip in man is possibly influenced, Scarff states, by the elaboration of complex functions of the upper extremities and the acquisition of speech.

"*Premotor Area*" versus "*Motor Area.*" Removal of Area 4 of the chimpanzee according to Fulton[20] results in immediate flaccid paralysis of all movements of the contralateral arm, the distal musculature being affected more than the proximal. While considerable improvement in function is noted following the operation, precise digital movements do not return. Although the paralysis is essentially flaccid in character, a

phase of digital spasticity has been noted between the 3rd and 5th postoperative week (Denny-Brown and Botterell[8]). The tendon reflexes disappear initially but soon return, and usually become somewhat hyperactive. Dorsiflexion of the great toe appears: eventually there is marked atrophy of the contralateral musculature, especially proximally.

When Area 6 is removed, the neurologic deficit presents a picture that is significantly different. This consists of transient contralateral paresis, permanent awkwardness with skilled movements, forced grasping, spasticity, and reflex changes. The paresis is slight and is present but for a few days following the ablation. The permanent defect with skilled movements is manifest in such actions as approximating the thumb and index fingernail or picking up a hair. Forced grasping is said to be due to withdrawal of extrapyramidal inhibitory impulses from this area which releases subcortical centers. It consists of the slow flexion of the digits in response to gentle contact with the palmar or plantar skin and is present in both primates and man following lesions of Area 6. It disappears in the course of a week in the monkey and in 2 weeks in the chimpanzee. Similarly, the spasticity and the moderate increase in tendon reflexes are transient events with ablations limited to this area, as are the presence of the Rossolimo toe reflex and the Hoffmann finger reflex. In spite of the fact that lesions of Area 4 result in an essentially flaccid type of palsy, it is only when removal of this area is added to that of Area 6 that all of the deficits described above become permanent and marked. The reflex changes are conspicuous and enduring and are essentially those which accompany the spastic state in man. The tendon reflexes are markedly increased, and pathologic reflexes (Babinski, Chaddock, Rossolimo, Hoffmann, Mendel-Bechterew, Gonda) are present. Forced grasping also becomes permanent and predictable.

Fulton chooses to call Area 6 the "premotor area" in contrast to Area 4, the "motor area." The justification for the use of this term is based on the different findings following ablation of each of the areas, the absence of Betz cells in Area 6, the decreased excitability to electrical stimulation of Area 6, and the loss of isolated motor responses from Area 6 after an incision is made between the two areas. It is assumed that isolated volitional movements depend upon Area 4 and its projection, the pyramidal tract. Gross movements, however, may originate from the premotor area and be transmitted over extrapyramidal pathways.

Walshe[54] has raised a number of objections not only to the term "premotor area" but to Fulton's concept of a dual motor mechanism as outlined above. These objections are summarized: (1) There is no sharp anatomic division between the two zones. As shown by Economo and Koskinas, the "hairline divisions" between Areas 4 and 6 do not rest on any certain anatomic foundation. (2) Stimulation experiments in both anthropoids and man (Leyton and Sherrington,[36] Foerster,[16] Penfield and Boldrey[46]) have given no indication of a difference in function between the two areas. "As the stimulating electrode passes anteriorly across the cortex of Area 4 (FA) on to that of Area 6 (FB), the character of the motor responses and the strength of stimulus necessary to evoke them show no change whatever except at the anterior fringe." The concept of discrete movements being dependent on Area 4 and of widespread movements on extrapyramidal projections from Area 6 is also attacked. Widespread movements obtainable from Area 6 may be the result of the increased strength of stimulus rather than any physiologic difference inherent in the two areas. As Foerster[16] has shown, wide regions of the cortex

can be made to yield movements on maximal stimulation. This does not prove that these areas normally give rise to such movement. "All that can be elicited from this supposed premotor cortex can also be elicited from the rest of the motor cortex if this be sufficiently strongly stimulated." (3) The evidence from ablations of Areas 4 and 6 is in such conflict that no conclusions may be drawn. He cites the occasional increase in reflexes and hypertonus in some of Fulton's animals in which Area 4 was removed and the lack of hypertonia in others in which Area 6 was removed. Denny-Brown and Botterell[8] have described an initial flaccidity and the subsequent development of spasticity and hyperreflexia in monkeys with only Area 4 removed. Foerster[16a] has said: "So far as conclusions can be drawn from these observations, they seem to demonstrate that the motor disturbance resulting from isolated destruction of Area 4 in man does not differ to a detectable degree from that due to destruction of both Areas 4 and 6aa." (4) Walshe argues that section of the pyramid in the medulla must interrupt both pyramidal and extrapyramidal fibers and therefore, if Fulton's hypothesis is correct, should lead to spasticity. The pyramidal tract lesions of Tower,[51] however, have resulted in a flaccid paralysis. This, according to Walshe, proves the incorrectness of the dual motor mechanism hypothesis. He fails to consider that the extrapyramidal tracts, which Fulton *et al.* believe to be responsible for spasticity, may course outside of the medullary pyramid. The postulation is made that interference with short projection tracts arising in Areas 4 and 6 (*i. e.*, the precentro-pontine tract, cortico-rubral and cortico-nigral tracts) are the responsible agents. "The extension of this field of cells well into Area FB (Area 6) in which its focus may well lie, may account for the marked hypertonus that ensues when ablations encroach upon the region immediately anterior to the motor cortex." As far as can be made out, the work of Fulton and his colleagues (see Kennard,[30b] 1944) does not contradict this point of view. It may well be that Walshe and they are actually not far apart in their views but that the difference is mainly one of terminology.

Suppressor ("Strip") Areas. Revision of the conclusions of Fulton and his collaborators have been necessitated by the work of Marion Hines[26a] (1937). She has shown that ablation of a slender strip of cortex in the anterior portion of Area 4 gives rise to all of the phenomena described by Fulton in his "premotor area syndrome" except that of forced grasping. In the rhesus monkey both release phenomena and paralysis appear in the extremity opposite the side of the lesion. The paralysis disappears, for the most part, within 2 weeks. Muscular hypertonus, clonus and hyperactive reflexes remain. As in the human with spastic hemiplegia, the maximal hypertonus is in the flexors of the elbow, the extensors of the knee and the adductors of the thigh. This "strip area" of Hines is about 3 mm. in width. "It passes through the superior precentral fissure. It extends from the superior precentral fissure to the fissura calloso-marginalis on the medial surface, following throughout at equidistance the curve of the central fissure." Isolated ablation of Area 6 by Hines leads to none of the findings described by Fulton for his "premotor syndrome" except the presence of the grasp reflex.

When both the "strip" area (4s) and Area 6 are removed, the distribution of muscular hypertonus changes and the "clasp knife" type of resistance seen with Area 4s lesions disappears. The hypertonus is present and similar in both protagonists and antagonists (flexors and

extensors) in the proximal joints of all four extremities. Brisk reflexes are present initially but gradually subside.

When the posterior portion of Area 4 is removed, a picture similar to that described by Fulton for removal of Area 4 appears. No spasticity or hyperreflexia is present. Paralysis is about complete for 2 days, then gradually disappears in 2 months. After total removal of Area 4 (including 4s), the contralateral limbs are not used to initiate voluntary movement but merely aid or follow those of the other extremities. Hyperreflexia, clonus and hypertonus are present, but the latter is not as marked as when the lesion is restricted to the strip area.

From this work and from stimulation experiments upon animals in which the medullary pyramids have been sectioned (Tower and Hines,[52] Tower[51]), Hines concludes that Area 6 is responsible for inhibition of flexor patterns (grasp reflex) and that the strip area (4s) is responsible for inhibition of extensor patterns. "The removal of the anterior division of Area 4 (the "strip" area) gave a maximum loss of inhibition of extension; its stimulation, relaxation of tonic extension. The removal of Area 6 gave the grasp reflex; its stimulation relaxation of tonic flexion including the grasp. The removal of both of these areas results in the relase of two opposing inhibitions which tend to neutralize each other, such that differential resistance to passive movement is lost; and resistance becomes distributed equally between protagonists and antagonists."

As demonstrated by these experiments and those following section of the medullary pyramids by Hine's co-worker, Tower,[51] spasticity and paralysis are distinct entities, the former being transmitted over extrapyramidal pathways, the latter—at least in part—over pyramidal pathways.

In a series of important experiments, Dusser de Barenne and McCulloch, later with Garol and Bailey,[1,9,10,23,24,40] have produced evidence that parallels that of Hines in regard to the function and connections of the strip area (4s). They have also shown that other "strip areas" with similar functions are present in the cortex of the macaque and the chimpanzee and have succeeded in tracing the pathways from these areas into the basal ganglia. Dusser de Barenne long ago demonstrated that when strychnine is applied locally to the central nervous system, disturbances are set up which travel along axons in the direction of normal conduction, not antidromically. These disturbances are diminished, dispersed and delayed when they pass through synapses. They may be recorded by means of electroencephalographic apparatus. It is therefore possible to delimit the axonal distribution of nerve cells in any gray mass of the central nervous system. This method has been termed "physiological neuronography."

Dusser de Barenne *et al.* have shown that stimulation of the anterior portion of Area 4 (4s) results in the diminution not only of the spontaneous electrical activity of Area 4 but also of peripheral motor responses. This "suppression" has a latent period of about 4 minutes. It has been shown using the strychnine method that suppression of electrical activity is not due to direct connections between Area 4s and Area 4, but rather to impulses which travel down to the caudate nucleus. From the caudate nucleus, the impulses are carried back to the cortex by means of an indirect pathway involving thalamo-cortical projections. Four other "suppressor areas" have also been described, 8s, 2s, 19s, and 24s. "The characteristic responses obtained from electrical stimulation of such suppressor areas, varying somewhat with the duration and intensity of stimulation, are as follows: (1) a lessening of existing muscular tension throughout the

body, particularly on the contralateral side; (2) a pronounced rise in threshold to electrical stimulation of Area 4; (3) a holding in abeyance of a motor after-discharge induced by stimulation of Area 4; (4) a failure to produce, in the absence of summation or recruitment, a peripheral motor response; and (5) a return of normal electrical excitability following suppression. These phenomena are abolished by undercutting of the area, *e. g.*, Area 4s." Suppression of motor response in man from stimulation of a circumscribed area of cortex has just been reported by Garol and Bucy.[23]

Parietal Lobe and Motor Function. The histologic evidence of giant pyramidal cells in the postcentral area, the work of Levin and Bradford[35] showing that about 20% of pyramidal fibers originate in Areas 3, 1, 2 and 5, and the descriptions of motor responses to electrical stimulation of the parietal lobe have been cited. No true paralysis has been reported with lesions confined to this lobe. Brodmann[4] and Ferraro and Barrera[13] have noted hypotonia following removal of the postcentral gyrus. Kennard and Kessler,[31] in a study of motor performance following parietal lobe ablations, have described a motor deficit characterized by disuse, diminished resistance to passive movement, non-persistent hyporeflexia and awkwardness of movement, the latter apparently being the result of losses in the sensory sphere. More recently Peele[45b] has described a "loathness of movement" in the macaque. Removal of Areas 3-1-2 affected the contralateral leg and arm equally. Removal of Area 5 affected the leg in particular, and removal of Area 7 the arm. Hypotonia was consistently present for as long as a year, especially involving the proximal muscles of both arm and leg. Tendon reflexes were more difficult to elicit, were slower and had an increased excursion.

In spite of the evidence that removal of either Area 4 or the postcentral gyrus (Areas 3-1-2) independently result in hypotonia or flaccidity, both Walker (cited by Fulton[20]) and Welch and Kennard[55] assert that combined lesions lead to spasticity. Welch and Kennard apparently attribute this curious phenomenon to the severance of additional extrapyramidal pathways, although they state that only relatively small extrapyramidal contingents arise from these areas. "All evidence presented is thus in harmony with the statement of Fulton who writes '. . . . the intensity and duration of spastic resistance are functions, not of any area, but of the extent of interruption of extrapyramidal cortical projections.'" Certainly the determination of the presence of flaccidity and spasticity is no simple arithmetical function. The flaccidity of the pyramidal lesion is not a nullifying influence upon the spasticity of the extrapyramidal lesion. To further complicate matters, Browder[5] reports that ablation of the human postcentral region reduces rather than enhances preëxisting spasticity.

Basal Ganglia and Motor Function. As might have been predicted from Hines' demonstration of a cortical inhibitory area (4s) and the subsequent demonstration by "physiologic neuronography" of connections between it and the caudate nucleus, recent evidence shows that one of the main functions of the basal ganglia is inhibition of cortically induced movements. Stimulation experiments upon basal ganglia structures have failed to give definite results. Mettler,[41a,42] as others before him, failed to produce any responses upon simple stimulation of either caudate, putamen or claustrum in the cat. When, however, phasic (repetitive) movements were produced by cortical stimulation, subsequent stimulation of these structures produced definite effects. Stimulation of the

caudate nucleus led to inhibition of these movements. Similar, though milder, results were obtained by stimulation of the putamen and claustrum. Freeman and Krasno[18] later showed that spontaneous activity was inhibited by striatal stimulation. While this inhibitory function appears to act bilaterally, there has not been general agreement as to the predominant side which is influenced. Mettler believed that the contralateral side is especially involved, while Freeman and Krasno believed homolateral inhibition is the more marked. Simple stimulation of the globus pallidum by Mettler resulted in tonic, postural contractures on the ipsilateral side, even when the cortex was removed or the pyramids cut. Following the production of cortically induced movement, stimulation of the globus pallidum converted this movement into a state of plastic tonus. Portions of the limb could be placed in any position and would remain fixed during the period of stimulation. In addition, relaxation time was greatly prolonged. Mettler therefore concludes, "The pyramidal and extrapyramidal systems constitute a closely organized and interrelated functional unit. Not only the final motorneuron but also the cortex forms ground common to these two so-called 'systems.' In this arrangement the striatum (caudate and putamen) occupies the position of an inhibitory mechanism. Stimulation of it produces inhibition and removal of it engenders evidences of motor release. It stands on the one hand between the cortex and the final common path as part of the route through which the cortex may exert an inhibitory function and, on the other hand, it operates between the thalamus and lower motor mechanisms in the automatic inhibition incident to 'unconscious' activity. The pallidum, as contrasted with the striatum, is a positive motor mechanism through which associated movement patterns involving the larger muscle masses . . . . are involved in tonic discharge."

Combined Lesions of "Motor" Area and Basal Ganglia. Lesions confined to basal ganglia have given equivocal results, as far as resistance to passive movement and reflex changes are concerned. (Discussion of the abnormal movements such as tremor and chorea from these lesions is omitted here.) Liddell and Phillips[37] have reported a slight but persistent hypertonia of the extensor muscles in the contralateral limbs. This has not been seen by Mettler[41a] or Kennard.[30b] Kennard and Mettler agree, however, in spite of the absence of spasticity with lesions restricted to basal ganglia, when such lesions are added to cortical ablations, there is a substantial increase in the spasticity. In a recent paper (1943) Mettler[41b] discusses in detail the results of such lesions in primates. With unilateral frontal decortication, paresis and spasticity are so mild "that they may be imperceptible to the inexperienced observer." With complete unilateral decortication there is no specific additional paralysis. When the striatum (caudate and putamen) is added to the decortication, there is little further loss of motor capacity except for loss of monomanual feeding with the involved hand. There is much less spasticity after hemidecortication alone than after removal of both cortex and striatum. In addition there is a reduction of the threshold and an increase in amplitude of the patellar reflex with combined removals. Only when the defect in the basal ganglia is extremely large, reaching the level of the posterior commissure, does paralysis become almost complete, and spasticity is of such a degree as to give rise to fibrous contractures.

The Plantar Reflex (Babinski Sign). Until recently there has been general agreement that the Babinski sign, dorsiflexion of the great toe following plantar stimulation, occurs only as a result of pyramidal tract

interruption. Fulton[20b] states that it is part of a generalized flexor reflex such as is seen in its full form in spinal animals. The typical response may be seen in the chimpanzee after removal of the foot area, according to Fulton and Keller.[21] The same observers stated that the typical Babinski sign does not occur in lower forms, such as the monkey. The absence of the response in Tower's monkeys in which the medullary pyramids were cut was explained on this basis. In 1942 Forster and Campbell[17] succeeded in producing the Babinski sign in a number of rhesus monkeys in which extensive cerebral damage had been produced. They concluded that extensive, bilateral cortical lesions may give rise to the phenomenon in the monkey and that the projection fibers may travel down the ventral columns of the spinal cord. In an extensive study of lesions of the brain stem in primates, Mettler[41c] (1944) has noted the pathologic toe response in animals without pyramidal tract involvement. Destruction of the rubro-spinal system was found to be most consistently associated with the Babinski response, even in the absence of paralysis. Mettler therefore suggests that this sign indicates extrapyramidal rather than pyramidal damage.

Additional evidence that the sign of Babinski and other so-called "pyramidal signs" may be the result of lesions outside the pyramidal tract has been presented by Lassek[32h] (1944). He studied the pyramidal tract in 119 clinical cases with "pyramidal signs," 100 of these having a Babinski response. In only 14% was there any observable evidence of destruction to this tract, and in only 6.7% was it complete. The Babinski sign was present in 88 of 102 cases in which the pyramidal tract was observed to be normal. A tumor mass in apparently any part of the cerebrum produced motor loss with either a transient or permanent Babinski sign. Lassek, therefore, could find no correlation between the Babinski sign and pyramidal tract damage.

Conclusions. Researches during the past decade have contributed a vast amount of information regarding the pyramidal tract, its relationship and its function. Much of this information is inconclusive and contradictory. Some of it has necessarily been destructive in the sense that it was mainly directed at disproving ancient dogma concerning the pyramidal tract, handed down through a number of medical generations.

The neurologist is placed in the unenviable position of being less sure about his knowledge of the motor system and less sure of his interpretation of motor deficits than he formerly was. It is no longer possible for him to state with any degree of assurance that spasticity, hyperreflexia and pathologic reflexes are certain evidences of pyramidal tract disease.

In spite of the almost inevitable confusion surrounding an adolescent field of investigation, certain conclusions may be drawn.

1. The pyramidal tract does not arise solely from the Betz cells of Area 4. These cells, not well-defined units in themselves, are far outnumbered by pyramidal axons. It seems most likely, though not definitely proven, that not only do Area 6 and the areas of the postcentral gyrus give rise to these fibers, but that they come from widespread cortical areas. It also seems likely that the pyramidal tract in the spinal cord (lateral corticospinal tract) is mixed with fibers originating in subcortical nuclei.

2. The pyramidal tract terminates for the most part, not upon the anterior horn cell (motoneuron) of the spinal cord, but upon internuncial neurons in the central gray matter. Here they are in a position to influence not only the lower motor neuron but also all sensory impulses entering

the cord over the dorsal roots. The physiologic implications of this are yet to be adequately analyzed.

3. Neither partial or total section of the pyramidal tract gives rise to spastic paralysis. Decreased resistance to passive movement without hyperreflexia appears to result.

4. The pyramidal tract is not the sole voluntary motor pathway. It is, however, apparently essential for the complete preservation of isolated, intricate and skilled movements.

5. The pyramidal tract is not an inhibitory pathway, as was propounded by Charcot. Inhibition, rather, is the function of extrapyramidal pathways originating in certain areas of the cortex, the caudate nucleus and probably elsewhere. Stimulation of these areas results in the inhibition of voluntary activity.

6. From the evidence available at present, it seems likely that hyperreflexia and spasticity are release phenomena from lesions of extrapyramidal pathways. This evidence is not completely convincing. Enduring hyperreflexia and spasticity are only seen with combined pyramidal-extrapyramidal lesions. The absence of hyperreflexia in basal ganglion syndromes such as paralysis agitans has not been elucidated.

7. The cerebral cortex is not divided into purely pyramidal and purely extrapyramidal areas just as it is not divided into purely motor and purely sensory areas. This complicated, overlapping functioning has not made analysis of the "motor cortex" easy. While Area 4 is undoubtedly the most significant in the production of movement, Area 6 and portions of the parietal lobe also play a rôle. The type of neurologic deficit which follows any cortical lesion appears to depend upon the relative impairment of pyramidal and extrapyramidal projections. Lesions of the posterior portion of Area 4 apparently lead to defects in isolated, precise movements, without spasticity or markedly increased reflexes. Lesions rostral to the posterior portion of Area 4 give rise to the release phenomena of spasticity and hyperreflexia. Combined lesions of Area 4 and the postcentral gyrus lead to similar findings. There is some evidence that Area 4s is responsible for inhibition of extension patterns and Area 6 for inhibition of flexor patterns.

8. The most marked and enduring spastic paralyses are seen when not only cortical motor projections are abolished but also large portions of the basal ganglia.

9. While a good deal of evidence still favors the concept that the Babinski response is due to a lesion of the pyramidal tract, this remains a moot question.

10. The suggestion is made that when one is confronted with the findings of hyperreflexia, clonus, spasticity and pathologic reflexes, that the term "pyramidal tract signs" be abandoned. As a substitute, the less specific "upper motor neuron signs" may be used, if this is meant to include both pyramidal and extrapyramidal pathways.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF NOVEMBER 21, 1944

Repair Following Tucking Operations on the Extra-ocular Muscles.* K. S. CHOUKE (Department of Anatomy, Graduate School of Medicine, University of Pennsylvania). Thirty-eight tucking operations were performed on either the superior rectus or the lateral rectus muscle of 20 adult dogs. Dogs varied in weight from 7 to 19 kg. The animals were sacri-

* Aided by Research Grant No. 503 of the Graduate Board of Education and Research, University of Pennsylvania.

ficed from 1 to 155 days after the operation. For anesthesia, sodium amytal was used intraperitoneally or intravenously.

The muscle union was accomplished by organization of fibrin and by granulation tissue. This observation confirms the findings of Carroll and Blake, and of Gifford.

After a tucking operation the 2 adjacent sides of the loop of muscle join together by means of fibrous connective tissue. The side of the muscle nearest the eyeball quite often, but not always, becomes attached to the sclera by fibrous connective tissue. The process of repair of extra-ocular muscles in the dog is essentially similar to that of the skeletal muscles elsewhere in the body. The time required for the completion of repair of extra-ocular muscles is slightly longer than that for general skeletal muscles of the same animal. The continuity of the muscle is preserved after the tucking operation, as evidenced by response to electrical stimulation.

The author gratefully acknowledges the preparation of the microscopic sections and the facilities for operation provided by the Harrison Department of Research Surgery, University of Pennsylvania, under the direction of Dr. I. S. Ravdin.

Chemotherapeutic Properties of Streptomycin. HARRY J. ROBINSON, OTTO E. GRAESSLE and DOROTHY G. SMITH (Merck Institute for Therapeutic Research, Rahway, N. J.). Recently we described the chemotherapeutic properties of streptothricin, an antibiotic agent isolated from a soil actinomycetes by Waksman and Woodruff. This agent proved to be highly active against gram-negative bacteria and pathogenic fungi (H. J. Robinson, O. E. Graessle, and D. G. Smith) but, unlike penicillin, streptothricin produced certain toxic effects in a variety of animal species. During the course of the study with streptothricin, a second agent was isolated by Schatz, Bugie and Waksman from *A. griseus* and was named streptomycin. We have studied *in vitro* and *in vivo* the pharmacologic, toxicologic, and chemotherapeutic properties of streptomycin, and the results of this investigation are presented in the following:

Streptomycin is well tolerated by mice and rats when given parenterally in doses of 50,000 units per kg. daily over a period of 1 month. Likewise, monkeys also tolerate large doses of the drug without showing any untoward reactions.

Streptomycin, *in vitro*, is active against a variety of gram-negative and gram-positive bacteria, but not against fungi. Members of the gram-negative enteric group of microörganisms and related genera, including Eberthella, Salmonella, Escherichia, Shigella, Klebsiella, Brucella, Pasteurella, and Proteus, are particularly sensitive to streptomycin, while certain strains of *Pseudomonas aeruginosa* show considerable resistance. Of the gram-positive organisms, strains of *Strep. hemolyticus*, *Staph. aureus* and *D. pneumoniæ* are sensitive to streptomycin, whereas all members of the spore-bearing anaërobic group are highly resistant. Experiments in mice gave essentially the same results, subcutaneous doses of 100 units per mouse protecting against 10,000 lethal doses of most of the foregoing bacteria.

Streptomycin is most effective when given parenterally, although it also protects mice infected by intraperitoneal injection when administered by mouth. Examination of the feces of mice fed streptomycin shows that adequate doses sterilize the gastro-intestinal tract insofar as lactose-fermenting organisms are concerned. The total microbial population of the feces is also reduced considerably.

Following parenteral administration approximately 70% of the drug appear in the urine within 5 to 6 hours after the injection. In order to maintain blood concentrations, it has to be administered by frequent intramuscular injection or by continuous intravenous drip.

The low toxicity and the effectiveness against both gram-negative and gram-positive bacteria suggest that streptomycin will prove a valuable chemotherapeutic agent.

Observations on the Function of the Lymphocyte. W. E. EHRICH and T. N. HARRIS (Depts. of Pathology and Pediatrics, Univ. of Penna. and Phila. Gen. Hosp). In a previous study of a limited and well-circumscribed system which included the hind foot of the rabbit (the site of injection), the lymph contained in the afferent lymph vessels, the popliteal lymph node (the only regional node to the site of injection), the efferent lymph, and finally the serum, it was shown that antibodies first appeared in the efferent lymph 2 to 4 days after injection of the antigen (typhoid bacilli, sheep erythrocytes) and reached their highest titer after 6 days. This antibody formation was preceded and accompanied by a marked rise in the output of lymphocytes in the efferent lymph and by hyperplasia of the lymphatic tissue within the lymph node. The fact that the cellular response was chiefly lymphocytic suggested that the lymphocyte may play an important rôle in antibody formation.

The present work rests upon the study of an even smaller and more isolated system, namely, the lymphocytes and the lymph plasma of the efferent lymph collected during the period of antibody formation. A comparison of the concentrations of antibodies contained in these two fractions revealed that 5 days after injection of the antigen the lymphocytes contained 8 or 16 times as much antibody as the lymph plasma. This observation offered only two possible interpretations, namely, that the lymphocyte either absorbs or adsorbs, or produces, antibodies. Normal lymphocytes were incubated with antibody-containing lymph plasma, as antibody-containing serum was injected into the living lymph node and lymph removed several hours later. In no case was it possible to show adsorption or absorption of antibodies by the lymphocyte. On the other hand, it was observed that the ratio between lymphocyte titer and lymph plasma titer was greatest on the 5th day when antibody formation was greatest, while 2 days later the ratio had dropped considerably. These findings seem to show that the lymphocyte produces, rather than absorbs or adsorbs, antibodies.

Carbon Monoxide Polycythemia. HEINRICH BRIEGER (Division of Industrial Hygiene, Hahnemann Medical College and Hospital). A series of experiments on dogs and men furnished additional information on polycythemia in acute and in chronic carbon monoxide intoxication. I. *Acute CO Intoxication.* Polycythemia occurred, though not invariably. On the contrary, even decrease of Hb and RBC was encountered in our animal experiments. Hb values and RBC did not indicate a noticeable effect of early spleen contraction on the circulating blood.

Significant polycythemia was a late effect of high blood saturation with CO. Its full development could be observed several days after the exposure long after all CO had disappeared from the blood. Reticulocytosis and appearance of normoblasts indicated a stimulation of the bone marrow. Permanent polycythemia developed in 1 dog.

The correlation coefficient between Hb and RBC was, as a rule, not significant. II. *Chronic CO Intoxication.* Dogs were exposed for 11 weeks to an air concentration of 0.0096 vol. % CO leading to a blood saturation of 20.1 % COHb. Exposure for 9 weeks increased the RBC significantly; Hb showed a definite trend toward a similar increase. The values decreased during continued exposure to and slightly below the original level respectively. In the 3 months following the exposure, Hb rose in several dogs; in 1 animal to a level suggesting polycythemia.

Onset, development, and degree of the polycythemia varied considerably in the individual dogs. Polycythemia did not prevent the noxious effects on the circulatory and nervous systems in either acute or chronic CO intoxication.

BOOK REVIEWS AND NOTICES

THE BABY MANUAL. A Practical Guide from Early Pregnancy Through the Second Year of Life. By HERMAN N. BUNDESEN, M.D. Foreword by THOMAS PARRAN, M.D., Surgeon-General, U. S. P. H. S. Pp. 590; 137 figs. New York: Simon & Schuster, 1944. Price, $3.00.

HERE is another baby-raising book, thicker than most. It displays a laudatory preface signed by the Surgeon-General of the U. S. P. H. S. and a note on the last page modestly crediting Dr. Bundesen with cutting Chicago's infant death rate in half. The contents consist essentially of an expansion of the controversial pamphlets distributed monthly by the Chicago Health Department, already published in parts in "Our Babies." The first half is expository, in simple narrative style; the second half asks and gives answers to some 1001 caretaking questions which may puzzle untutored mothers. In internal arrangement one finds "books" on (1) Prenatal Care; (2) Care of the Baby; (3) The Premature Baby; and (4) The First Two Years. By and large, the contained information is clear and in accord with modern practices. The discussion on how to promote the flow of breast milk is especially good. The many illustrations, all photographic, have been carefully planned to emphasize the points being made, though the one on page 85 is incorrect, for the infant's stomach 3 hours after a feeding is empty and contracted, or nearly so, not hyperdistended with air like a small blimp. The major fault of the book is that it says too much. In countless places the Author steps beyond the proper realm of pediatric nursing into the provinces—dangerous for parents—of diagnosis, treatment and formula-writing. He offers specific instructions on feeding regulation, including when to wean, how to construct infant feeding mixtures according to body weight and age in months, when, which, and what dosage of vitamins to feed. He directs parents how to diagnose and prescribe for such diseases as boils, scabies, head lice, impetigo, middle ear infection, diarrhea, mumps, and chickenpox. Though the text is liberally sprinkled with statements counseling that "the doctor" be consulted about this or that difficulty, the selfsame paragraphs usually give explicit advice regarding the complaints in question. One can see that many a penny-wise and cocksure layman will lean upon this book with its generalizations in place of taking his child to a pediatrician or family physician for periodic examinations and individualized guidance. Amateur learning can be highly dangerous, especially for baby health. The justification given by both Dr. Bundesen and Dr. Parran is the shortage of civil practitioners during these war years. But the military emergency is temporary, whereas the book will go on and on, especially if it sells well, and defects minimized now will assume normal stature soon again. Therefore, though this book would prove helpful to graduate nurses active in infant welfare, to medical students working in pediatric dispensaries and to isolated missionaries and ranchers wanting to rear their families by modern methods, it is not likely that doctors who see infants at monthly intervals will welcome such an ill-planned body of information being placed in parents' hands.

I. W.

HIPERTENSION ARTERIAL NEFROGENA. By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCIOLO, LUIS F. LELOIR, JUAN M. MUNOZ, and ALBERTO C. TAQUINI, Instituto de Fisiologia de la Facultad de Ciencias Medicas de Buenos Aires; Instituto de cardiologia Fundacion V. F. Grego. Pp. 462; 93 figs. Buenos Aires: Liberia y Editorial "El Ateneo," 1943.

FOR those interested in reviewing the investigative work on hypertension reported during the past decade, this book will serve as an excellent guide.

XUM

It emphasizes the point of view of the Authors who, with B. A. Houssay, have performed numerous experiments along the same lines as those done by Page and his associates in this country. The first 3 chapters deal with the various methods of producing experimental hypertension and the pathology, pathogenesis, and abnormal physiology of animals so affected. Then follow discussions of renin, hypertensinogen and hypertensin. Finally, there are adequate discussions of the relationships between experimental hypertension and essential hypertension in man, and of the medical and surgical aspects of the treatment of hypertension. The bibliography refers to 1104 papers, drawn chiefly from the American literature. W. J.

A Source-Book of Biological Names and Terms. By Edmund C. Jaeger, Riverside Junior Coll., Riverside, Calif. Pp. 256. Springfield, Ill.: Charles C Thomas, 1944. Price, $3.50.

To those who are interested in the structure of biologic terms for etymologic or semantic reasons, and to those who find the literal meaning of a word useful in comprehending and teaching new knowledge, this book will be satisfying and instructive. "Students of medicine and dentistry, veterinarians, foresters, ranger-naturalists, quarantine officers, crop inspectors, paleontologists, physiologists, entomologists, biologists, botanists, zoölogists, mycologists, technical workers in special scientific fields, and laymen who have as a hobby a scientific subject, will find it a book constantly useful. . . . . Teachers of Latin and Greek interested in teaching the derivation of words useful to science students will find here a veritable storehouse of useful information. Scientists will find it a ready and rich source of word elements useful in coining new names."

The opening pages, which should be read carefully by those intending to use the book, give insight into the philosophy of word building. One sees, for instance, how the same root may enter into a number of compound words with different, yet correct, endings (*e. g.*, 16 different yet correct combinations of kalos and mus [beautiful mouse] are offered from actual usage). The book also helps toward better spelling and pronunciation of scientific tongue-twisters.

Though thousands of word elements are presented, yet they were carefully chosen and offered as merely illustrative; also, as it is a source-book, definitions are not included. For each word or stem, the derivation and examples are given, literally interspersed with space-saving symbols. One should not be surprised at the great frequency of insect species and genera. E. K.

Poisonous Plants of Hawaii. By Harry L. Arnold, M.D., F.A.C.P., Chief of Medical Service, The Queens Hosp., Honolulu. Pp. 71; 24 full-page illus. Honolulu, Hawaii: Tongg Publishing Co., 1944.

This privately printed booklet—the outgrowth of an earlier article that is now out of print—presents first the common and dangerous plants known to have caused serious poisoning; and then a larger number of plants listed by various authors as dangerous. The numerous full-page illustrations should be helpful in identification.

This should be a valuable book for the inhabitants of Hawaii, and for sojourners there. E. K.

Textbook of Rehabilitation, Re-education and Remedial Exercises. By Olive F. Guthrie Smith, M.B.E., C.S.M.M.G., T.M.G., Principal of the Swedish Inst., London, Director of the Physical Exercise Depart. of St. Mary's Hosp., Member of the Council of the Chartered Society of Physiotherapists. Foreword by Lord Horder, G.C.V.O., M.D., F.R.C.P. Pp. 424; 273 figs. Baltimore: Williams & Wilkins, 1943. Price, $6.00.

This book follows the current trend of adding more strenuous exercises to the older, conservative procedures of physiotherapy. It is of particular

interest at present when there is emphasis upon the rehabilitation and reconditioning of soldiers. Information is presented in a manner which is at once clear and concise, yet in sufficient detail to be easily understood and put into practice.

The book covers 3 principal topics, as the title indicates. Following a discussion of rehabilitation, the Author describes the more strenuous exercises, and leaves the subject of passive treatments for the final chapters. The part played by suspension therapy is well illustrated. A. R.

THE MEDICAL CLINICS OF NORTH AMERICA. New York Number. SYMPOSIUM ON PSYCHOSOMATIC MEDICINE. By 18 Contributors. Pp. 787; 62 figs. Philadelphia and London: W. B. Saunders, 1944.

THIS New York number, a symposium on Psychosomatic Medicine, includes in its list of contributors: Dr. Leland E. Hinsie, Dr. Rene A. Spitz, Dr. Nolan Lewis, Comdr. A. M. Master, U.S.N.R., Dr. Asher Winkelstein, Dr. George E. Daniels, Dr. J. Louise Despert, Drs. James S. Greene and S. Mouchly Small, Drs. John Romano and George L. Engle, Dr. Milton Erickson, Dr. Flanders Dunbar, Dr. John J. Moorhead, and Dr. Alvan L. Barach.

The volume also contains additional clinics on "Symptoms Referable to Digestive Organs Resulting from Diseases of Abdominal Blood Vessels" by Dr. I. W. Held; "Medical Ophthalmologic Aids and Practice" by Dr. Ferdinand L. P. Koch; "Rocky Mountain Spotted Fever" by Dr. George E. Baker.

In addition to the diversity of subjects touched in the Symposium on Psychosomatic Medicine, the general reader has at his command a storehouse for ready reference in psychosomatic field. For the most part, for a general audience the participants have expressed themselves in a neatly understood fashion. H. B.

GLOBAL EPIDEMIOLOGY, A Geography of Disease and Sanitation. By JAMES STEVENS SIMMONS, B.S., M.D., PH.D., DR.P.H., SC.D. (HON.), Brigadier General, U.S.A., Chief Preventive Medicine Service, Office of the Surgeon-General, U.S.A.; TOM F. WHAYNE, A.B., M.D., Lieut. Col., M.C., A.U.S., Formerly Director, Medical Intelligence Division, Preventive Medicine Service, Office of the Surgeon-General, U.S.A.; GAYLORD WEST ANDERSON, A.B., M.D., DR.P.H., Lieut. Col., M.C., A.U.S., Director, Medical Intelligence Division, Preventive Medicine Service, Office of the Surgeon-General, U.S.A., Director, School of Public Health, University of Minnesota; HAROLD MACLACHLAN HORACK, B.S., M.D., Major, M.C., A.U.S., Chief Dissemination Branch, Medical Intelligence Division, Preventive Medicine Service, Office of the Surgeon-General, U.S.A.; Instructor in Medicine, Duke University School of Medicine; and Collaborators. Vol. 1, Part 1: India and the Far East; Part 2: The Pacific Area. Pp. 504. Philadelphia: J. B. Lippincott, 1944. Price, $7.00.

THERE is a definite need for a study of this type, due to the fact that men of our armed forces are stationed throughout the world, and are constantly returning to this country. We are presented with Volume One which covers India, the Far East, and the Pacific area. Other volumes will undoubtedly follow.

This book is a compilation of studies drawn up much in the fashion of the War Department Technical Bulletins which have appeared on the medical and sanitary data of the various countries and islands. These bulletins and the material of this book were based on the studies made by the Medical Intelligence Division, Preventive Medicine Service, Office of the Surgeon-General. Each country and island is taken up in turn with a discussion of the geography and climate, public health service, water supply, sewage disposal, vectors of disease, food and dairy products, problems of sanitation, hospital and medical facilities, and disease incidence.

This work will be chiefly of value as a reference volume. It will be useful to those treating our returning soldiers and to those pioneers of industry who may already be planning reconstruction or the opening up of new industries in the Far East.

The book is well presented with frequent small diagrams showing occurrence of disease within the various localities. Each section is complete with bibliography. D. P.

DISEASES OF THE DIGESTIVE SYSTEM. Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P., Associate Professor of Medicine, University of Illinois Med. School (Rush); Attending Physician, Michael Reese Hosp.; Consulting Physician, Cook County Hosp.; Consultant in Medicine to the Inst. of Psychoanalysis, Chicago. Second Ed. Pp. 932; 182 illus. Philadelphia: Lea & Febiger, 1944. Price, $11.00.

THIS second edition of the first comprehensive textbook in English on the diseases of the entire digestive system will be welcomed by teachers, practitioners and students. The first edition met a distinct need, but recent progress in the field necessitated more than a revision. Even now certain sections, such as that on epidemic hepatitis, need revision and elaboration. No textbook, however, can be entirely up to date. The chief merits of this one are its all-inclusiveness, the emphasis which has been placed on the functional aspects of gastro-enterology and the relationship of digestive disturbances to disease in other systems of the body. The 50 contributors are well known in connection with the subjects they discuss and their names add weight to the opinions expressed. An ample bibliography accompanies each chapter, the illustrations are excellent, and the general arrangement of the subject matter enhances its value for reference. M. H.

CATARACT AND ANOMALIES OF THE LENS. Growth, Structure, Composition, Metabolism, Disorders, and Treatment of the Crystalline Lens. By JOHN G. BELLOWS, M.D., PH.D., Assistant Professor of Ophthalmology, Northwestern Univ. Med. School, Chicago. Pp. 624; 208 figs.; 4 color plates. St. Louis: C. V. Mosby, 1944. Price, $12.00.

THE material in this book includes everything of importance that is known today about the animal and human lens. Almost all of this material could be found elsewhere either in textbooks or in ophthalmologic literature; but the Author brings together here in one volume a great deal of information of reference value heretofore scattered in many volumes, probably the chief contribution made by this publication. Not the least of this material is that which is derived from the Author's own researches in recent years, particularly on the chemistry and metabolism of the lens and on experimental cataracts. The accompanying bibliography is extensive. The volume is not essential to all, but is a valuable addition to any well-rounded ophthalmologic library. F. A.

RECENT ADVANCES IN ANÆSTHESIA AND ANALGESIA (Including Oxygen Therapy). By C. LANGTON HEWER, M.B., B.S. (LOND.), D.A. (ENG.). Fifth ed. Pp. 343; 141 figs. Philadelphia: Blakiston, 1944. Price, $5.50.

THIS fifth edition of a popular, compact handbook, written by an authoritative British worker, primarily reflects the English point of view. As a consequence, certain characteristics are evident. Description of apparatus is more of local than of general interest. The references are largely European; and, finally, current ideas are those of the British group. The advantages of this type of presentation in broadening an American's knowledge are obvious. Some new material has been added since the 1943 edition, but this is not striking. R. D.

THE URINARY TRACT. A Handbook of Roentgen Diagnosis. By H. DABNEY KERR, M.D., Professor of Radiology, State Univ. of Iowa Coll. of Medicine, and CARL L. GILLIES, M.D., Associate Professor of Radiology, State Univ. of Iowa Coll. of Medicine. Pp. 320; numerous figs. Chicago: Year Book Publishers, 1944. Price, $5.50.

THIS volume fills a long existing need for a concise, informative reference on the use of the Roentgen ray in urologic diagnosis. The clinical material was gathered from the records of the University of Iowa Hospital. Illustrations are well selected and excellently reproduced.

The book is divided into 4 major sections: the kidney, ureter, bladder, and urethra. Under each of these sections the normal roentgenologic appearance of the organ is given. All practical methods of study are used. Because no 2 lesions, or normal structures, are alike, the authors show several examples of every condition wherever possible. Following illustrations of the normal appearances of the organs are those of all common abnormal conditions, such as stone, tumor, non-specific infection, tuberculous infection, congenital anomalies, and traumatic lesions. Many illustrations of uncommon lesions are also given.

Adequate radiographic study is an important factor in diagnosis of urologic disease. One cannot study this book without realizing this fact. However the Authors emphasize the fact that in determining the status of the urinary tract it is necessary to correlate all clinical and laboratory data with the Roentgen findings before making a final diagnosis.

As a text and as a reference, this book should be of value to students, practitioners, and specialists. L. La T.

X-RAY EXAMINATION OF THE STOMACH. A Description of the Roentgenologic Anatomy, Physiology, and Pathology of the Esophagus, Stomach, and Duodenum. By FREDERIC E. TEMPLETON, M.D., Head of the Dept. of Roentgenology, The Cleveland Clinic; Formerly Associate Professor of Roentgenology at the Univ. of Chicago. Pp. 516; 297 figs. Chicago: Univ. of Chicago Press, 1944. Price, $10.00.

THIS book contains 18 chapters on the Roentgen examination of the pharynx, esophagus, stomach and duodenum. It considers all of the various details concerned with those examinations, including the apparatus, the media, the technique of the examination and the basic principles of interpretation. It also includes the anatomy, physiology, and pathology of the various structures. The title is unfortunate in that it does not convey to the reader the content of the text. The subtitle is much more accurate.

The Author has considered in an erudite manner all phases of the Roentgen examination of the pharynx, esophagus, stomach and duodenum, drawing on both his own experience and many excellent articles on this subject. His consideration of the anatomy and physiology of the part, as determined experimentally by the Roentgen examination and by other methods, makes the book well worth reading. It will be most useful not only to the inexperienced radiologist but to the more experienced radiologist and teachers in anatomy, physiology, and radiology.

The paper used by the publisher is good; the illustrations are excellent, and for the most part the format of the book is satisfactory. There are some features in the format of the book that are not conventional and one suspects that the shortage of paper may be the explanation. The Reviewer refers to the fact that Chapter 1 includes the Introduction and on page 3 the first chapter is finished and it immediately starts into Chapter 2—The Apparatus.

The Reviewer was much surprised to see such a poor index for such an excellent text. It does not in any way convey what there is in the text. If properly indexed, this book would take many more pages.

Likewise, the Reviewer was somewhat surprised to see the improper use of roentgenologic terms. For instance, frequently the word film is used where the Author is referring to a roentgenogram. Likewise, the word *x*-ray is used

where the Author refers to the Roentgen examination or the *x*-ray examination. These criticisms are minor. The book is an excellent contribution and will serve a most useful purpose. E. P.

MEDICAL CLINICS OF NORTH AMERICA. The Mayo Clinic Number. SYMPOSIUM ON CHEMOTHERAPY. By 36 Contributors. Pp. 789–1028; 75 figs. Philadelphia and London: Saunders, 1944. Price, $16.00 per year.

THIS edition contains 2 parts: the first covers the clinical usages of the sulfonamides in general medicine and the specialties; the second consists of numerous articles on miscellaneous subjects of both medicine and surgery as covered by specialists at the Mayo Foundation.

Common problems encountered in the course of treatment are covered, both with the older sulfonamides and the newer drugs, including sulfamerazine, sulfamethazine and sulfasuxidine. A broad field of treatment is opened to the general practitioner through the clinics given on the sulfonamides in the specialties—ophthalmology, otolaryngology, urology and pediatrics.

The second part contains a number of articles, both interesting and useful with respect to keeping a busy doctor abreast of recent developments. Of special appeal are the articles on the peripheral blood count and the clinic occurrence of eosinophilia. J. W.

ANNUAL REVIEW OF BIOCHEMISTRY. By JAMES MURRAY LUCK, Editor, Stanford Univ., and JAMES H. C. SMITH, Associate Editor, Carnegie Inst. of Washington, Division of Plant Biology, Stanford Univ., California. Vol. 13. Pp. 795. California: Stanford Univ. P. O., Annual Reviews, Inc., 1944. Price, $5.00.

THE 1944 edition follows the same general plan as the previous volumes, and for the most part the same subjects are covered, including oxidations and reductions, enzymes, chemistry and metabolism of carbohydrates, fats and proteins, nutrition, and so on. As usual, there are a few subjects in this volume which have either been reviewed at infrequent intervals or are making their appearance for the first time. Among these may be mentioned the chapter on The Nutritional Deficiencies in Farm Animals on Natural Feeds, by C. F. Huffman and C. W. Duncan; a chapter on Photoperiodism in Plants, by K. C. Hammer; one on Chloroplast Pigments, by H. H. Strain, and one on Histochemistry, by D. Glick. The reviewers of these last-named subjects have not confined themselves to the most recent literature but have presented their subjects more in the form of general reviews.

Like the other volumes of this series there is a surprising absence of typographical errors, and in every other respect this volume meets the high standard set by the previous numbers. J. J.

TABER'S DICTIONARY OF GYNECOLOGY AND OBSTETRICS. By CLARENCE WILBUR TABER, Medical Editor and Author of Taber's Cyclopedic Medical Dictionary, Taber's Condensed Medical Dictionary, and Dictionary of Food and Nutrition, etc. With the Collaboration of MARIO A. CASTALLO, M.D., F.A.C.S., Assistant Professor of Obstetrics, Jefferson Med. Coll.; Gynecologist to St. Mary's and St. Agnes' Hosps.; Obstetrician to St. Mary's Hosp.; Diplomate, American Board of Obstetrics and Gynecology, etc. Pp. 706; numerous illus. Philadelphia: F. A. Davis, 1944. Price, $3.50.

DEFINITIONS are of fundamental importance in any subject; but are of special value to students, teachers and writers. Therefore, Taber's Dictionary is most welcome, especially to those who teach in the fields of gynecology and obstetrics. This volume, although it is built around definitions, is more than a mere dictionary. Many of the subjects which it lists are much more fully treated than is the case with the usual dictionary. In addition, it contains a number of useful illustrations. In my opinion, it should be in every library dealing with the subjects it covers. D. M.

THE MEDICAL CLINICS OF NORTH AMERICA. SYMPOSIUM ON SPECIFIC METHODS OF TREATMENT. The Boston Number. 22 Contributors. Pp. 1292; 96 figs. Philadelphia & London: Saunders, 1944. Price, $16.00 a yr.

THIS number is made up of a series of discussions on the management of certain outstanding medical and psychomatic problems. The articles are clearly written and several contain charts useful in summarizing the material presented. Penicillin and thiouracil, as newer therapeutic agents, are included; also, by Stanley Cobb, a technique for interviewing a patient with a psychomatic disorder. Chester M. Jones discusses the functional gastro-intestinal disturbances, and Edward C. Reifenstein presents a very helpful and practical paper on endocrinology. Three articles on pediatrics (acute bronchiolitis, adenoid bronchosinusitis and chronic diarrhea) are included. The treatment of diseases of the heart and of the kidney is covered, respectively, by Paul D. White and George W. Thorn. Altogether this is a very readable and useful book.

M. H.

OUR AMERICAN BABIES. The Art of Baby Care. By DOROTHY V. WHIPPLE, M.D. Introduction by C. ANDERSON ALDRICH, M.D., Chief of Staff, The Children's Memorial Hosp., Chicago. Pp. 367; numerous figs. and tables. New York: M. Barrows, 1944. Price, $2.50.

THIS new guide to baby care is one of the finest to appear in recent years. It is clear, direct, readable, and packed with homespun counsel of the most practical sort. Dr. Whipple has 3 children of her own (whose faces presumably appear in some of the colorful photographs which contribute so much to the appeal of the book), and she writes from experience gained both as a pediatrician and as a mother. There are 6 sections: Preparing for the First Baby; As the Baby Grows; Food and Feeding; Keeping the Baby Well and Happy; Prevention and Treatment of Disease in Babies and Young Children; The Baby's Grownups. Advice and instruction are given not only on such exclusively bodily matters as breast feedings, cuts and wounds, the fitting of shoes, and enema-giving—to cite but a few instances—but on more domestic problems such as buttons *versus* ties on baby garments, metal *versus* glass drinking cups, companionship with the father, birthday parties, and "the art of being a grandmother."

I. W.

COLORIMETRIC DETERMINATION OF TRACES OF METALS. By E. B. SANDELL, PH.D., Assistant Professor of Analytical Chemistry, Univ. of Minnesota. Vol. 3. Pp. 487; 73 figs.; 66 tables. New York: Interscience Publishers, 1944. Price, $7.00.

THIS excellent monograph is the third volume of a current series upon Chemical Analysis. In it Dr. Sandell presents clearly a great many sensitive chemical methods which have been devised for the determination of trace metals. The work happily meets a real need for a collection under one cover of information which heretofore has been most difficult to find without arduous search through scattered original literature.

Trace metals are of great importance not only in industry, as for example in the analysis for impurities in steel, but also in biology. The list of trace metals of interest to the biologist concerned with metabolism or pathology is constantly growing. Such a list includes iron, copper, zinc, manganese, aluminum, cobalt, nickel, lead, arsenic, bismuth, and mercury. It is gratifying that the Author has included, for all the above, techniques adapted to biologic material.

Preliminary chapters are devoted to general procedures such as adsorption and to the methods of colorimetry (photometry), spectrophotometry, and fluorimetry. This material is presented briefly, and perhaps somewhat sketchily. On the whole, however, the book is a more than adequate summary of the field which it covers and is highly recommended by the Reviewer.

D. D.

EXPERIMENTAL SPECTROSCOPY. By RALPH A. SAWYER, PH.D., Professor of Physics, Univ. of Michigan; now Lt. Comdr., U.S.N.R., and on leave from the Univ. of Michigan. Pp. 323; 107 figs. New York: Prentice-Hall, 1944. Price, $6.00.

THE review of a book upon spectroscopic techniques would have appeared out of place in a medical journal some years ago. That such a review is presented at this time is an indication of the ever-increasing overlapping of the various branches of science. The Author has produced a short text, crammed full of facts, based largely on his own extensive experience. The book is clearly written and very readable. The lucidity of presentation probably accounts for its small size. All technical matters of importance are dealt with adequately. It is to be regretted that only a very brief chapter is devoted to spectrochemical analysis, a field in which Commander Sawyer has been personally concerned. It is to be hoped, also, that in a revision of this work more space may be devoted to absorption spectrophotometry, at present of greater primary interest to biologists than line spectra. The Reviewer believes that this excellent book may well become a standard work in its field.

D. D.

ALL ABOUT FEEDING CHILDREN. By MILTON J. E. SENN, M.D., Associate Attending Pediatrician, New York Hosp.; Associate Professor of Pediatrics in Psychiatry, Cornell Univ. Med. Coll.; and PHYLLIS KRAFFT NEWILL. Pp. 269. New York: Doubleday, Doran & Co., 1944. Price, $2.50.

THIS manual, produced by the joint collaboration of a skilled dietitian and a pediatrician specializing in child psychiatry, discusses the myriad facets of the feeding of normal children. The best picture of the content is given by the list of chapter headings: "Good Nutrition Is Every Child's Birthright; Establishing the Young Infant's Feeding Schedule; The Breast-Fed Baby; The Bottle-Fed Baby; Preparing Special Formulas; Some Feeding Facts That Grandma Didn't Know; Dysfunctions Associated With Eating; Foods for Your Baby's First Year; Feeding the Child Between 1 and 2 Years old; Feeding the Child Between 2 and 6 Years Old; Feeding Children Between 6 and 12 Years Old; Eating With the Family; Equipment for Preparing Your Child's Food; Water; Cod-Liver Oil and Other Vitamin-D Sources; Cereals, Breadstuffs, and Macaroni Products; Eggs; Vegetables; Fruits; Meat, Fish, and Poultry; Soups; Sweets and Desserts; Fats; Salads and Salad Dressings; Milk and Milk Products in the Diet of Older Children; Beverages; Special Diets and Foods Your Physician May Order; Parties, Picnics, and Holidays; The School Lunch Box; Traveling With Young Children; Food and the War." The recipes and instructions for the choice and preparation of foods supplement nicely the dissertations on the psychologic aspects of the giving and eating of the foods.

This book will appeal equally to mothers, to school dietitians and to physicians whose practices include children. It is well planned, thorough, readable, and excellent in all respects.

I. W.

NEW BOOKS

Trichinosis. By SYLVESTER E. GOULD, M.D., D.Sc., Pathologist and Director of Laboratories, Eloise Hosp., Eloise, Mich.; Assistant Professor of Pathology, Wayne Univ. Coll. of Med., Detroit. Pp. 356; 128 figs. Illinois: Thomas, 1945. Price, $5.00.

A Bibliography of Aviation Medicine. Supplement. By PHEBE MARGARET HOFF, EBBE CURTIS HOFF, and JOHN FARQUHAR FULTON. Publication No. 9, Historical Library, Yale Medical Library. Pp. 109. Illinois: Thomas, 1944. Price, $2.50.

The Biological Basis of Individuality. By LEO LOEB, Professor Emeritus of Pathology, Washington Univ. School of Med., St. Louis. Pp. 711. Illinois: Thomas, 1945. Price, $10.50.

The Experiments of Nature and Other Essays. By IRVINE MCQUARRIE, PH.D., M.D., Dept. of Pediatrics, The Medical School, Univ. of Minnesota, Minneapolis, Minn. Delivered at the Univ. of Kansas School of Med., Lawrence, Kansas City. Porter Lectures, Series 12. Pp. 115; 16 figs. Kansas: Univ. of Kansas, Univ. Extension Division, 1944.

Crime and the Human Mind. By DAVID ABRAHAMSEN, M.D., Dept. of Psychiatry, Columbia Univ. Pp. 244. New York: Columbia Univ. Press, 1944. Price, $3.00.

Medical Clinics of North America. Philadelphia Number. Symposium on Recent Advances in Medicine. Pp. 1293 to 1608. Index for 1942–1944. Philadelphia and London: Saunders, 1944. Price, $16 per year.

Control of Pain in Childbirth. By CLIFFORD B. LULL, M.D., F.A.C.S., Clinical Professor of Obstetrics, Jefferson Med. Coll.; Assistant Director, Phila. Lying-In Unit, Penna. Hosp.; and ROBERT A. HINGSON, M.D., Surgeon, U. S. Public Health Service; Director, Post-graduate Medical Course, Phila. Lying-In Unit, Penna. Hosp. With an introduction by NORRIS W. VAUX, M.D., Obstetrician-in-Chief, Phila. Lying-In Unit, Penna. Hosp. Pp. 356; 100 illus., 32 subjects in color. Philadelphia: Lippincott, 1944. Price, $7.50.

The Art of Resuscitation. By PALUEL J. FLAGG, M.D., Chairman, Comm. on Asphyxia, Am. Med. Assn.; President and Founder of the Soc. for the Prevention of Asphyxial Death, Inc.; Director of Pneumatology, New York World's Fair, 1939, Inc.; Author, "Art of Anæsthesia"; Visiting Anesthetist, Manhattan Eye and Ear Hosp.; Consulting Anesthetist to St. Vincent's Hosp., The Woman's Hosp., Sea View Hosp., Jamaica Hosp., Mount Vernon Hosp., Flushing Hosp., Mary Immaculate Hosp., St. Mary's Hosp. and Nassau Hosp. Pp. 453; 176 figs. New York: Reinhold, 1944. Price, $5.00.

Outline of the Amino Acids and Proteins. Edited by MELVILLE SAHYUN, M.A., PH.D., Vice-President and Director of Research, Frederick Stearns & Co., Detroit, Mich. Contributing Authors: HENRY B. BULL, WILLIAM M. CAHILL, HERBERT E. CARTER, DAVID M. GREENBERG, MICHAEL HEIDELBERGER, IRVING R. HOOPER, CARL L. A. SCHMIDT, C. F. KADE, ARMAND J. QUICK, MELVILLE SAHYUN, ARTHUR H. SMITH, MADELYN WOMACK, DEAN LAURENCE. Pp. 251. New York: Reinhold, 1944. Price, $4.00.

Laboratory and Clinical Studies. Vol. XXIV. From the Memorial Hosp. for the Treatment of Cancer and Allied Diseases. Forty-one Contributors. New York, 1943.

Large Scale Rorschach Techniques. A Manual for the Group Rorschach and Multiple Choice Test. By M. R. HARROWER-ERICKSON, ACAD.DIP., PH.D., Research Associate, Dept. of Neuropsychiatry, Univ. of Wisconsin; and M. E. STEINER, B.A., M.A., Personnel Section, General Electric Co., Bridgeport, Conn. Pp. 420; 47 tables; 70 illus. Illinois: Thomas, 1945. Price, $8.50.

Handbook of Industrial Psychology. By DR. MAY SMITH. Pp. 304. New York: Philosophical Library, 1944. Price, $5.00.

Soldier to Civilian. Problems of Readjustment. By GEORGE K. PRATT, M.D., Psychiatric Examiner, U. S. Armed Forces, Induction Center, New Haven, Conn.; Formerly Assistant Clinical Professor of Psychiatry, School of Med., Yale Univ. Foreword by GEORGE S. STEVENSON, M.D., Medical Director, The National Committee for Mental Hygiene. Pp. 231. New York and London: Whittlesey House, McGraw-Hill, 1944. Price, $2.50.

NEW EDITIONS

Foundations of Neuro-psychiatry. By STANLEY COBB, A.B., M.D., Bullard Professor of Neuropathology, Harvard Med. School; Psychiatrist in Chief, Massachusetts General Hosp. Third ed. Pp. 252; numerous figs. Baltimore: Williams & Wilkins, 1944. Price, $2.50.

Elements of Electrocardiographic Interpretation. By LOUIS N. KATZ, A.M., M.D., Director of Cardiovascular Research, The Michael Reese Hosp., Chicago; Professorial Lecturer in Physiology, The Univ. of Chicago; and VICTOR JOHNSON, PH.D., M.D., Professorial Lecturer in Physiology, The Univ. of Chicago. Third ed. Pp. 44; 40 plates illustrating the more important deviations from the normal, selected from the files of the Michael Reese Hospital. Illinois: The Univ. of Chicago Press, 1944. Price, $1.00.

Clinical Practice in Infectious Diseases. For Students, Practitioners and Medical Officers. By E. H. R. HARRIES, M.D. (LOND.), F.R.C.P., D.P.H., Medical Supt., North-Eastern Hosp. (London County Council); Formerly Med. Supt., City Hosp., and Univ. Clinical Lecturer in Fevers, Birmingham; Milroy Lecturer, Royal Coll. of Physicians, London; and M. MITMAN, M.D. (LOND.), M.R.C.P., D.P.H., D.M.R.E., Med. Supt., River Hosps.; Formerly Med. Supt., Eastern Hosp., and Divisional Medical Officer, Public Health Dept., London County Council. With a Foreword by W. ALLEN DALEY, M.D. (LOND.), F.R.C.P., D.P.H., Medical Officer of Health, London County Council. Second ed. Pp. 570; 26 tables; 52 figs. Edinburgh: E. & S. Livingstone, 1944. Price, $6.00.

Arthritis and Allied Conditions. By BERNARD I. COMROE, A.B., M.D., F.A.C.P., Associate in Medicine, Univ. of Penna.; Senior Ward Physician and Chief of the Arthritis Clinic Hosp. of the Univ. of Penna. Third ed., enlarged and thoroughly revised. Pp. 1359; 329 illus. Philadelphia: Lea & Febiger, 1944. Price, $12.00.

Symptoms of Visceral Disease. A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.F., Medical Director, Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, Calif.; Professor Emeritus of Clinical Medicine, Univ. of Southern California; Author of "Clinical Tuberculosis," "Tuberculin in Diagnosis and Treatment," "Muscle Spasm and Degeneration," etc. Sixth ed. Pp. 442; 87 illus. and 10 color plates. St. Louis: Mosby, 1944. Price, $5.00.

Contagious Diseases. A Guide for Parents. By W. W. BAUER, B.S., M.D., Director, Bureau of Health Education, Am. Med. Assn.; Associate Editor, *Hygeia, The Health Magazine;* Formerly Epidemiologist, Milwaukee Health Dept.; Lecturer in Public Health, Marquette Univ. Commissioner of Health, Racine, Wis. Second ed. Pp. 188. New York: Knopf, 1944. Price, $2.00.

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